Predicting Acute-on-Chronic Liver Failure in Cirrhosis (PREDICT) study;Addendum ancillary study:
Inflammation, endothelial dysfunction and macro- and microvascular flow in acute decompensation of of cirrhosis and acute-on-chronic liver failure

Published: 11-04-2017
Last updated: 13-04-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal conditions NEC
Study type	Observational invasive

Summary

ID

NL-OMON50182

Source
ToetsingOnline

Brief title
PREDICT study

Condition

- Gastrointestinal conditions NEC
- Hepatic and hepatobiliary disorders
- Encephalopathies

Synonym
acute decompersation of a cirrotic liver - liver failure

Research involving
Human

Sponsors and support

Primary sponsor: European Foundation for the study of chronic liver failure (EF CLIF)
Source(s) of monetary or material Support: EASL-CLIF Consortium

Intervention

Keyword: ACLF, Cirrhosis, Decompensation, Liver

Outcome measures

Primary outcome

* 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

Addendum ancillary study:

1) Endothelial, microvascular and macrovascular function by repeated measurement of microvascular flow using sublingual sidestream-darkfield imaging and forearm blood flow using Doppler-ultrasonography

2) Markers of endothelial cell activation (VWF:Ag, VWFpp, ADMA), systemic vasoconstrictor systems (i.e. copeptin, renin and noradrenaline) and inflammation markers (CRP, leucocytes)

Secondary outcome

* 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.

Study description

Background summary

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. 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.

During the CANONIC study, the largest study so far including prospectively patients with acute decompensation of cirrhosis (AD), the predisposing factors, clinical and laboratory predictors for the development of ACLF have been studied. The CLIF-C AD score was developed to discriminate the patients with high-risk of ACLF within three months. Taking advantage of this knowledge the current study PREDICT will screen patients with AD and without ACLF at initial admission, but will investigate more in detail patients with almost 50% risk of developing ACLF within 3 months (CLIF-C AD score * 60).

Addendum ancillary study:
Systemic inflammation plays a key role in the development of acute-on-chronic liver failure (ACLF). Bacterial translocation across the intestinal barrier in advanced cirrhosis promotes the release of pro-inflammatory molecules, thereby leading to inflammation. An acute increase in systemic inflammation is thought to be the primary event in developing ACLF. This results in cardiovascular dysfunction, organ hypoperfusion and organ inflammation. Patients with cirrhosis are known to have peripheral vasodilatation and a reduced responsiveness to exogeneous administered vasoconstrictor agents. Inflammatory mechanisms like the activation of the host innate immune response may trigger endothelial molecular mechanisms, which possibly contribute to arterial vasodilation. It is presently unknown whether inflammation is related to micro- or macrovascular dysfunction in patients with acute decompensation of cirrhosis (AD) or ACLF. We aim to measure forearm blood flow and sublingual microvascular flow and endothelial surface layer (ESL) in order to determine whether blood flow and ESL are associated with markers of endothelial cell activation, inflammation and systemic hemodynamics in patients with AD or ACLF.

Study objective

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).
collective of patients will be screened out of cirrhotic patients admitted to hospital with acute decompensation (ascites, overt encephalopathy, GI-hemorrhage, new onset of non-obstructive jaundice and/or bacterial infections) but without the presence of ACLF. Thus this study aims to collect detailed data (including health trajectory) and diverse biological materials from these patients in order to uncover the pathophysiological mechanisms associated with ACLF and the time-line of the development of ACLF. Moreover, using cutting-edge technologies and prospective ancillary studies PREDICT will identify predictors and potential biomarkers for the development of ACLF.

SPECIFIC GOALS:
* 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 (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.

Addendum ancillary study:
Protocol 1) To determine endothelial, microvascular and macrovascular function in patients with (high-risk CLIF-C * 60) AD to assess the relationship between vascular function and outcome (development of ACLF, mortality)
Protocol 2) To assess markers of endothelial cell activation, systemic vasoconstrictor systems and inflammation in the critical period prior to the development of ACLF to predict the development of vascular dysfunction, ACLF and outcome.

Study 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. 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.
3. Prospective collection of biological material and performance of ancillary studies investigating predictors for development and pathogenesis of ACLF.

Addendum ancillary study:
Protocol 1) Two-dimensional Doppler echocardiography and vascular function measurements will be obtained by a dedicated radiologist. The average of 5 subsequent measurements will be used at every time point. Sublingual microcirculatory density and flow will be monitored using sidestream dark field (SDF) imaging. Briefly, a hand-held video microscope system that epi-illuminates with stroboscopic green (530 nm) light-emitting diodes will be positioned gently on the sublingual mucosa on the mouth at the base of the

tongue. Video*s, during at least 10 seconds, from five different sites will be recorded. Repeated assessments will be performed between 5 and 10 days after the day of inclusion in the Predict study. If a patient develops ACLF according to the criteria from the CANONIC study (16), assessment of microvascular and macrovascular blood flow is repeated at time of development of ACLF, and between day 5 and 10 after development of ACLF. Twelve weeks after inclusion in the PREDICT study the Doppler ultrasound measurements will be repeated.

Protocol 2) A pilot study consisting of 200 patients participating in the PREDICT study (including the 40 patients from protocol 1) will be performed. Centrally randomly selected patients admitted for AD>60 with (n=100) and without (n=100) ACLF development during follow-up will be included in study protocol 2. VWF:Ag and VWFpp, ADMA and markers of endogenous vasoconstrictor systems will be measured in samples drawn at hospital admission. In total, 900 µl blood (50 µl serum, 600 µl EDTA plasma, 200 µl 3.2% sodium citrate plasma and 50 µl heparin plasma) will be sampled at baseline.In the group of patients who developed ACLF during follow-up a second measurement of these biomarkers will be performed at time of onset of ACLF and 5-8days after development of ACLF.

Study burden and risks

There are no anticipated risks associated with this study. The patients will not receive any direct benefit from participation. There is no guarantee or promise that patients will receive any benefits from this study.

Addendum ancillary study:
There are no anticipated risks associated with this ancillary study. The patients will not receive any direct benefit from participation. There is no guarantee or promise that patients will receive any benefits from this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

The patients admitted/referred to study center with acute decompensation 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. , Addendum ancillary studie:
Protocol 1) 40 patients admitted to the PREDICT study centers in UCL, London, UK, LUMC, Leiden or Alrijne Ziekenhuis, Leiderdorp, The Netherlands, with high-risk CLIF-C * 60 acute decompensation 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.
Protocol 2) A pilot study consisting of 200 patients participating in the PREDICT study (including the 40 patients from protocol 1) will be performed. Centrally randomly selected patients from all participating centers admitted for AD>60 with (n<=100) and without (n<=100) ACLF development during follow-up will be included

Exclusion criteria

1. Patients with acute or subacute liver failure without underlying cirrhosis;
2. Evidence of current malignancy except for non-melanocytic skin cancer and hepatocellular carcinoma within Milan criteria;
3. Previous liver or other transplantation
4. Admission/referral of more than 72 hours before inclusion , Addendum ancillary studie:

No informed consent for participation in the PREDICT study

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-05-2017
Enrollment:	52
Type:	Actual

Ethics review

Approved WMO

Date:	11-04-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	17-06-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	27-02-2020

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL60470.058.17

Study results

Date completed:	22-02-2021
Actual enrolment:	44

Summary results
Trial is onging in other countries