Liver transplantation in patients with CirrHosis and severe Acute-on-Chronic Liver Failure (ACLF): iNdications and outComEs (CHANCE)

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1. Primary objective: Survival results of LT in patients with severe ACLF To compare 1-year graft and patient survival rates after LT in patients with ACLF-2 or 3 at the time of LT with patients with decompensated cirrhosis without ACLF 2-3 and…

Ethical review	Approved WMO
Status	Pending
Health condition type	Hepatic and hepatobiliary disorders
Study type	Observational invasive

Summary

ID

NL-OMON52056

Source
ToetsingOnline

Brief title
CHANCE

Condition

- Hepatic and hepatobiliary disorders

Synonym
Cirrhosis and severe acute-on-chronic liver failure (ACLF)

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: EF-Clif

Intervention

Keyword: Acute-on-Chronic Liver Failure (ACLF), cirrhosis, transplantation

Outcome measures

Primary outcome

Primary endpoint

1-year graft and patient survival rates after liver transplantation

Secondary outcome

Secondary endpoints

Pre-Liver transplantation

Waiting time (from the listing to LT, days)

Mortality rate on the waiting list

Delisting rate on the waiting list

Clinical course (resolution/improvement/stabilization/worsening) of ACLF on the waiting list (evolution of grades, number of organ failures)

Incidence of ACLF development in patients listed without ACLF

Resources utilization on the waiting list

Post-Liver transplantation

3-month and 6-month graft and patient survival rates after liver transplantation

Hospital length of stay after LT (days)

ICU length of stay after LT (days)

3-month and 1-year health-related quality of life (HRQoL) after LT (by Chronic

Liver Disease Questionnaire [CLDQ] and EQ-5D)

3-month, 6-month and 1-year rate of dependency of renal replacement therapy or

kidney transplant

Resources utilization of LT and post-LT follow-up

Study description

Background summary

Patients with acute decompensation of cirrhosis are a heterogeneous clinical group associated with different prognoses which need to be stratified to define appropriate management. The term *Acute-on-Chronic Liver Failure (ACLF)* characterizes a subgroup of patients with chronic liver diseases which develop organ failure(s) leading to very poor short-term outcome. Several tools for estimating outcomes of patients with ACLF have been developed.
The management of ACLF per se is mainly supportive with intensive monitoring and supports of failing organs. Clinical deterioration despite maximal supportive management is associated with very poor outcomes and leads physicians to consider potential salvage liver transplantation (LT).
This option remains highly controversial. LT in sicker recipients is unquestionably associated with an improved survival benefit but could result in less acceptable longer-term survival rates after LT. Due to the scarcity of deceased liver donors, we need a strategy of rationing where the success of deceased-donor LT (DDLT) will be maximized.
A Patients listed with ACLF-3 has a high probability to die on the waiting list (WL) or be removed from the WL. Thus, we must define predictive factors of death or removal from the WL for patients with severe ACLF based on prospective data to try to design better rule for organ allocation for this group of patients. This especially in the context of scarcity of liver donors, the potential benefit of LT in ACLF patients must also be balanced against the need for rationing of limited resources.
Prospective data from large multicenter international studies are urgently needed, aiming to resolve objectively this controversial ethical issue that results either in wasting scarce organ resources or in precluding severely sick patient*s access to life-saving treatment.

This CHANCE study aims to develop new biomarkers to predict the prognosis on

the waiting list and after LT for patients with decompensated cirrhosis with or without ACLF-2 or 3, to investigate the impact of LT on systemic disturbances (inflammation, leukocyte dysfunction, metabolic alterations, dysbiosis) observed in ACLF and to explore the mechanisms of liver and extrahepatic organ recovery after LT in patients with ACLF-2 or 3 and determinants of this recovery.

Study objective

1. Primary objective: Survival results of LT in patients with severe ACLF

To compare 1-year graft and patient survival rates after LT in patients with ACLF-2 or 3 at the time of LT with patients with decompensated cirrhosis without ACLF 2-3 and transplant-free survival of patients with ACLF-2 or 3 not listed for LT.

2. Secondary objectives

1) To define the factors in decision-making process for listing patients with severe ACLF; in particular to assess the proportion of patients with ACLF-2 or 3 referred to transplant team who are listed or not and reasons of not listing.
2) To analyze the clinical course of patients listed with ACLF-2 or 3 on the waiting list compared with those of patients listed with decompensated cirrhosis without ACLF-2 or 3.
3) To define independent predictive factors of death/delisting on the waiting list for patients listed with ACLF-2 or 3 and develop a new prognostic model based on ACLF criteria to predict mortality on the waiting list and to improve the allocation of organs.
4) To compare the characteristics of accepted grafts for patients listed with ACLF-2 or 3 with those of patients listed with decompensated cirrhosis without ACLF-2 or 3 and their impact on post-LT outcomes.
5) To explore independent predictive factors of death after LT for patients transplanted with ACLF-2 or 3 to design futility criteria for LT.
6) To compare post-LT survival rates of patients with ACLF-2 or 3 at listing and patients without ACLF at listing who develop ACLF-2 or 3 on the waiting list.
7) To compare post-LT quality of life (QoL) for patients listed with ACLF-2 or 3 with those of patients listed with decompensated cirrhosis without ACLF-2 or 3.
8) To assess the resources utilization of care and LT procedure in patients listed with ACLF-2 or 3 (in intention-to-treat and per protocol) compared with patients listed with decompensated cirrhosis without ACLF-2 or 3.

3. Exploratory objectives

1) To develop new biomarkers to predict the prognosis on the waiting list and after LT for patients with decompensated cirrhosis with or without ACLF-2 or 3.
2) To investigate the impact of LT on systemic disturbances (inflammation, leukocyte dysfunction, metabolic alterations) observed in ACLF.
3) To explore the mechanisms of liver and extrahepatic organ recovery after LT in patients with ACLF-2 or 3 and determinants of this recovery.
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Study design

Prospective non-interventional observational study

Study burden and risks

The current study does not pose any significant risk to the patients and the only burden is collection of blood, urine, liver tissue and saliva.
The study has no direct benefit for the included subjects. The results of this study may result in a substantial improvement in knowledge about pathogenesis, prognosis and treatment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Male or female subject >=18 years of age.
2. Subjects with diagnosis of liver cirrhosis (based on clinical, laboratory, endoscopic, and ultrasonographic features or on histology).
3. Subjects who have been hospitalized for acute decompensation of liver cirrhosis and referred to the transplant team:
o Group 1: patients listed for liver transplantation with ACLF-2 or 3 at the time of listing or developing ACLF 2-3 while on the waiting list.
o Group 2: patients listed for liver transplantation with decompensated cirrhosis without ACLF-2 or 3 and poor liver function (MELD>20) at the time of listing.
o Group 3: patients having ACLF-2 or 3, are assessed for inclusion in the waiting list, but are finally not listed for liver transplantation.
4. Patients (or trusted person, family member or close relation if the patient is unable to express consent) who have been informed and signed their informed consent

Exclusion criteria

1. Acute or subacute liver failure without underlying cirrhosis.
2. Patients with hepatocellular carcinoma outside Milan criteria or other active neoplasia.
3. Subjects listed for transplantation other than liver or liver-kidney transplant.
4. Subjects with previous liver transplantation.
5. Vulnerable population (person under temporary or permanent guardianship or deprived of liberty by a judicial decision).
6. Pregnant and/or breastfeeding woman
7. Patients with relevant comorbidities that could impact the prognosis:
o Subjects with very severe hepatopulmonary syndrome (with PaO2 < 50 mmHg on FiO2 21%) or moderate to severe portopulmonary hypertension (non-reversible mPAP >= 35 mmHg or PVR >= 500 dyn.s.cm-5).
o Subjects with severe (grade IV) pulmonary disease (Global Obstructive Lung Disease [GOLD]).
o Subjects with chronic kidney disease requiring hemodialysis

o Subjects with severe heart disease (NYHA class III and IV)
o Subjects with a known infection with human immunodeficiency virus (HIV)
o Subjects with severe neurological or psychiatric disorders
8. Patients 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.
9. Physician and team not committed to provide intensive care if needed.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2021
Enrollment:	105
Type:	Anticipated

Ethics review

Approved WMO

Date:	30-05-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
ClinicalTrials.gov	NCT04613921
CCMO	NL77933.078.21