EF Clif
EUROPEAN FOUNDATION FOR THE STUDY OF CHRONIC LIVER FAILURE

Study published in the Journal of Hepatology

Researchers from EF Clif identify the causes that precipitate the onset of the most serious stage of cirrhosis: the syndrome of Acute-On-Chronic Liver Failure

• In 96% of cases, bacterial infections and severe alcoholic hepatitis lead to acute decompensated cirrhosis and its most severe form, the Acute-on-Chronic Liver Failure (ACLF). Other precipitating events are gastrointestinal bleeding with hypovolemic shock and toxic encephalopathy.

• The precise identification of precipitating events is mandatory for subsequent development of preventive and therapeutic strategies that specifically address the causes of these pathologies and improve patient survival.

• These results are part of the second investigation from the PREDICT study, which aims at identifying predictors of and clinical mechanisms to prevent and treat ACLF.

• 136 researchers from 47 hospitals in 15 European countries participate in the study, led and coordinated from Barcelona by the EF Clif.

Barcelona, December 9th, 2020. A new investigation of the PREDICT study, which was led and coordinated from Barcelona by Prof. Jonel Trebicka, MD, PhD, (Goethe University Frankfurt) a clinical researcher of the *European Foundation for the Study of Chronic Liver Failure* (EF Clif), identifies that **bacterial infections and severe alcoholic hepatitis**, both independently and in combination, are the main precipitants that cause the development of acute decompensated cirrhosis and Acute-on-Chronic Liver Failure (ACLF), the most serious phase of cirrhosis.

ACLF occurs **in up to 96% of the cases analysed**, according to the results of this work published in the *Journal of Hepatology* and carried out within the framework of the **PREDICT study**, a prospective, observational, European-wide project that seeks to identify the clinical course of decompensation with the aim of predicting the development of the **ACLF syndrome**. The research has involved 136 researchers from 47 hospitals in 15 European countries from the EASL-CLIF Consortium.

Up to now, it was thought that acute decompensation in cirrhosis was initiated due to a severe worsening of stable cirrhosis, as a consequence of different precipitating events. In 2013 the **CANONIC** study characterized the **ACLF syndrome** as the most severe phenotype of acute decompensated cirrhosis. Recently, the first investigation of the **PREDICT** study demonstrated that acute decompensated cirrhosis manifests through different clinical phenotypes. Many investigations from both studies demonstrated that systemic inflammation induces multiple organ dysfunction and results in the different clinical phenotypes such as Pre-ACLF and ACLF.

The investigation of the PREDICT study led by investigators of the EF Clif was aimed at **diagnosing the main precipitating events of acute decompensated cirrhosis** and investigated the association of their type and quantity with the early clinical course and **prognosis** in hospitalized patients with acute decompensated cirrhosis, with or without ACLF. EF Clif-Researchers have identified a **set of precipitating events** that cause a **different prognosis and clinical course** in patients with acute decompensated cirrhosis. In addition **to proven bacterial infections and severe alcoholic hepatitis**, **gastrointestinal bleeding with hypovolemic shock and toxic encephalopathy** are also relevant.

Regarding the influence of the precipitating events on **the mortality of patients with acute decompensated cirrhosis and ACLF**, the researchers detected that the number of identifiable events is associated with an increase in mortality at 90 days. To the contrary, the type of precipitating event does not influence patient survival.

Improving the treatment of patients with acute decompensated cirrhosis

The discovery made by the group of researchers led by EF Clif opens the door to an improvement in the management of these patients. Taking into account that more than 96% of them showed proven bacterial infection and / or severe alcoholic hepatitis as the main precipitating events, independently or in combination with other factors, the results suggest that **diagnosing, preventing and treating these causes are essential to improve the prognosis in acute decompensated cirrhosis**.

Furthermore, the study shows that **adequate first-line antibiotic treatment of proven bacterial infections** is associated with a lower rate of ACLF development (21.3% vs 39.2%). This is a novel and remarkable finding according to Javier Fernandez (Hospital Clinic Barcelona, Clinical researcher at EFClif) the shared first authorship and expert in infections. Moreover, adequate first-line antibiotic therapy was associated with a lower mortality at 90 days, both in patients with acute decompensated cirrhosis (16.9% vs 36.5%) and in patients with ACLF (44.2% vs 66.2%).

Jonel Trebicka, principal investigator of the PREDICT study at the EF Clif stated that "the identification of these precipitating events allows us to approach the diagnosis of patients with greater certainty, developing specific preventive and therapeutic strategies aimed at controlling the precipitating events that we have detected and ultimately improve their quality of life ".

To read the article ***PREDICT identifies precipitating events associated with the clinical course of acutely decompensated cirrhosis***, by Jonel Trebicka, Javier Fernández, […], Rajiv Jalan, Vicente Arroyo and collaborators click on the following link https://www.journal-of-hepatology.eu/article/S0168-8278(20)33772-7/fulltext

The PREDICT study

The PREDICT study was designed to prospectively observe acutely decompensated patients at risk of developing ACLF over a 3-month period. Prospective ancillary studies have discovered predictors and pathophysiological, clinical and laboratory mechanisms involved in the development and clinical course of ACLF, with the aim of helping prevent and treat the condition.

A project in which 47 organizations and institutions from 15 European countries participate

The working team of the study, led by EF Clif, is made up of 136 researchers from European University Hospitals (See complete table of institutions in annex).

About decompensated cirrhosis and ACLF syndrome

Acute-on-chronic liver failure (ACLF) represents the most serious phase of cirrhosis, characterized by intense systemic inflammation in which patients develop failure of different organs or systems. ACLF is the main cause of death in cirrhotic patients and has a great socioeconomic impact, due to the high volume of health resources that the treatment requires and because it incapacitates the patient from work. The syndrome was described for the first time in 2013 by the same authors of the PREDICT study (Moreau R, Jalan R, Ginès P, Pavesi M, Angeli P, Cordoba J, et al. *Acute-on chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis*. Gastroenterology 2013; 144). Currently, it is understood that mortality is due to decompensated cirrhosis, characterized by the appearance of complications such as ascites, gastrointestinal bleeding and disorders of brain function that can lead to hepatic coma and which usually progress to ACLF.

Recent research led by the European Consortium for the Study of Chronic Hepatic Failure has shown that ACLF is a highly complex disorder appearing in patients with liver cirrhosis. In addition to the liver failure, cardiovascular, renal, and brain function, pulmonary, intestinal, adrenal and immune system may fail in these patients. It is, therefore, a special form of multi-organ failure.

The probability of survival after the onset of the syndrome is low, since it is associated with high short-term morbidity (30% at 28 days) and the only treatment at present is liver transplantation.

About the EF Clif

The European Foundation for the Study of Chronic Liver Failure (EF Clif) is a non-profit private foundation (President and Director: Prof. Vicente Arroyo, MD, PhD; Scientific Director: Prof. Rajiv Jalan, MD, PhD, (University College London); General Manager: Anna Bosch, PhD). Its mission is to promote study and research in hepatic chronic failure, intended to contribute to improving the quality of life and survival of patients with hepatic cirrhosis.

The EF Clif was founded in 2015 to support the research work carried out by the European Consortium for the Study of Chronic Liver Failure (EASL-Clif Consortium). The EASL-Clif Consortium is a research network made up of more than 100 European university hospitals and 200 clinical researchers. In 2013, the Consortium described a new syndrome: The Acute-on-Chronic Liver Failure (ACLF), which is the most common cause of death in cirrhosis.

Currently, EF Clif's research activity is supported by the Data Management Center (Head: Marco Pavesi) and promoted through two chairs: the EASL-Clif Chair (Prof. Paolo Angeli, MD, PhD University of Padova), to foster observational, pathophysiological and therapeutic studies through the EASL-Clif Consortium network of hospitals; and the Grifols Chair (Chairs: Prof. Richard Moreau, MD, PhD (Hopital Beaujon Paris); Prof. Joan Claria, PhD (Hospital Clinic Barcelona)) , which works on the development of translational research projects, by creating a network of centres throughout Europe: The European Network for Translational Research in Chronic Liver Failure (ENTR-CLIF).

For more information on EF Clif: Twitter: @ef_clif

About the Journal of Hepatology

The Journal of Hepatology is the official publication of the European Association for the Study of the Liver (EASL). It publishes original papers, reviews, case studies and letters to the editor referring to clinical and basic research in the field of hepatology. Its impact factor is 20,582.

www.journal-of-hepatology.eu

Attention to the media: include contact

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ANNEX: LIST OF INSTITUTIONS PARTICIPATING IN THE STUDY

Institution	City	Country
European Foundation for Study of Chronic Liver Failure, EF-Clif	Barcelona	Spain
JW Goethe University Hospital	Frankfurt	Germany
University Hospital Bonn	Bonn	Germany
Hospital Clinic	Barcelona	Spain
University of Debrecen, Faculty of Medicine, Institute of Medicine, Department of Gastroenterology	Debrecen	Hungary
University of Bologna	Bolonia	Italy
University of Padova	Padova	Italy
A.O.U. Città della Salute e della Scienza Torino	Turín	Italy
Hospital Universitari Vall d´Hebron	Barcelona	Spain
UCL Medical School,Royal Free Hospital	Londres	United Kingdom
C.U.B. Erasme	Bruselas	Belgium
Hospital Universitario Ramón y Cajal	Madrid	Spain
University of Leuven	Lovaina	Belgium
Hospital General Universitario Gregorio Marañón	Madrid	Spain
Pavol Jozef Safarik University in Kosice,	Kosice	Slovakia
Munich University Hospital	Munich	Germany
Medical University of Vienna,	Viena	Austria
Derriford Hospital, Plymouth Hospitals Trust	Plymouth	United Kingdom
Internal Medicine PO Ostuni, ASL Brindisi	Brindisi	Italy
King's College Hospital	Londres	United Kingdom
University Hospital Halle-Wittenberg	Halle(Saale)	Germany
University Hospital Leipzig	Leipzig	Germany
Jena University Hospital	Jena	Germany
Hvidovre University Hospital	Copenhague	Denmark
Leiden University Medical Center	Leiden	The Netherlands
Universitá Sapienza Roma	Roma	Italy
Medical University of Graz	Graz	Austria
Medical University of Innsbruck	Innsbruck	Austria
CHTMAD Vila Real-Blueclinical	Vila Real	Portugal
Hospital de la Santa Creu i Sant Pau and CIBERehd	Barcelona	Spain

University Clinic of Visceral Surgery and Medicine-Inselspital, Bern and Ente Ospedaliero Cantonale, Universita della Svizzera Italyna	Lugano	Switzerland
Aarhus University Hospital	Aarhus	Denmark
AP-HP Hôpital Paul Brousse, Centre Hépato-Biliaire, Universite Paris Saclay, INSERM Unit 1193	Villejuif	France
Aachen University Hospital, Aachen, Germany,	Aachen	Germany
Marmara University, Kadiköy, Turkey,	Kadiköy	Turkey
University Hospital Antwerp	Amberes	Belgium
NIHR Biomedical Research Centre at Nottingham University Hospitals NHS Trust and the University of Nottingham	Nottingham	United Kingdom
AP-HP, Hôpital Jean Verdier, Service d'Hépatologie, Bondy; Université Paris 13, Sorbonne Paris Cité, "Equipe labellisée Ligue Contre le Cancer", Saint-Denis; Inserm, UMR-1162, "Génomique fonctionnelle des tumeurs solides"	París	France
Hospital Universitario Virgen del Rocío	Sevilla	Spain
Ghent University Hospital	Gante	Belgium
APHP, Hôpital Beaujon, Service d'Hépatologie	Clichy	France
Inserm, Université de Paris, Centre de Recherche sur L´Inflammation	París	France
Hannover Medical School	Hannover	Germany
Munster University Hospital	Münster	Germany
University of Basel-St Gall Cantonal Hospital	Basel-St Gall	Switzerland
Hôpitaux Universitaires de Genève	Ginebra	Switzerland
University of Birmingham	Birmingham	United Kingdom