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1.  **MISSION, VISION AND VALUES**

The EF Clif is intended to support high quality research and education on *Acute on Chronic Liver Failure*, in order to improve the quality of life and to increase the survival of patients with *liver cirrhosis*. Our aim is helping investigators to achieve their objectives and being a referent in *Acute on Chronic Liver Failure* research.
2. OUR ORGANISATION

EF Clif Executive Scientific Committee
Coordinator / Scientific Director
General Manager
Chairman EASL Chair
Chairman Grifols Chair

EASL CHAIR

BOARD OF TRUSTEES

CLIF CONSORTIUM

STEERING COMMITTEE

STEERING COMMITTEE
(to be constituted)

ENTR

CLIF

DATA MANAGEMENT CENTRE

BIO-REPOSITORY

SCIENTIFIC FACILITIES

3. BOARD OF TRUSTEES

Vicente Arroyo M.D.
Emeritus Professor of Medicine, University of Barcelona Medical School, Spain.
Chairman of the EASL Clif Consortium.
Recognition Award, European Association for the Study of the Liver.
Main research interest
Chronic Liver Failure, ascites, acute bacterial infection in cirrhosis and Acute-on-Chronic Liver Failure.

Mauro Bernardi M.D.
Professor of Internal Medicine at Bologna University, Italy.
Director, Postgraduate School in Internal Medicine.
Treasurer, European Association for the Study of the Liver.
Vice-Chairman of the EASL Clif Consortium.
Distinguished Service Award, Italian Association for the Study of the Liver.
Main research fields
Cirrhosis and related complications, hepatocellular carcinoma, chronic viral hepatitis, liver transplantation clinical aspects and treatment of alcoholism.

Antoni Páez M.D. B. Sc.
Director, Medical & Technical Department. Grifols Bioscience Industrial Group.
Graduated in Medicine and Surgery from the Autonomous University of Barcelona.
Graduated in Physical Science. Open University (United Kingdom).
Main research fields
New functions of plasma proteins.

Ignacio Calero Lawyer
Lawyer at Osborne Clarke.
Graduated in Law from the Autonomous University of Madrid.
Masters Degree in Corporate Legal Advice from the Instituto de Empresa Business School (Madrid, 2000).
Main research fields
Chronic Liver Failure, ascites, acute bacterial infection in cirrhosis and Acute-on-Chronic Liver Failure.
4. THE EASL CHAIR

EASL CLIF CONSORTIUM STEERING COMMITTEE

The scientific activities of the network of hospitals organized in the setting of the EASL Chair are performed under the direction of a Chairman and a Vice-Chairman and of an EASL-Clif Consortium Steering Committee of 15 additional members.

Paolo Angeli
University of Padova
(2018-2022 Chairman of the EASL Clif Consortium)
Frederik Nevens
Ghent University Hospital, Leuven
Marco Pavesi
EF Clif, Barcelona
Mauro Bernardi
Politecnico S. Orsola-Malpighi, University of Bologna
Thomas Reiberger
Medical University of Vienna
Alexander Gerbes
Munich University Hospital
Francesco Salerno
Poliklinico San Donato, University of Milan
Faouzi Saliba
Hôpital Paul Brousse, Villejuif
Fin Stolze Larsen
Rigshospitalet, University of Copenhagen
Jonel Trebicka
Bonn University Hospital
Julia Wendon
King’s College Hospital, London
Reiner Wiest
University Clinic of Visceral Surgery and Medicine-Inselhospital, Bern

5. THE GRIFOLS CHAIR

EUROPEAN CLIF NETWORK OF TRANSLATIONAL RESEARCH (CLIF-ENTR). GOVERNING BOARD

The scientific activities of the European Clif Network of Translational Research centres, organized in the setting of the Grifols Chair are performed under the direction of a Director, a Deputy Director and a Secretary.

Director
Vicente Arroyo
EF Clif, Barcelona
Deputy Director
Richard Moreau
Hôpital Beaujon, Clichy
Secretary
Joan Clària
Hospital Clínic, Barcelona
6. OUR STAFF

MANAGEMENT
Managing Director
Anna Bosch
Josep Mª Torner
Administrative Assistant
Montserrat Carreras
Cecilia Ducco
Scientific Assistant
Yolanda Godoy

DATA MANAGEMENT CENTRE
Head
Marco Pavesi
Data Manager
Anna Curto
Carme Deulofeu
Cristina Sánchez
Statisticians
Ferran Aguilar
Àlex Amorós
Anna Curto
Elisabet García
Carla Pitarch

RESEARCH ASSOCIATES
PI Predict Study
Jonel Trebicka
PI Apache and Preciosa Study
Javier Fernández
Grifols Chair Coordinator
Joan Clària

7. FACTS AND FIGURES

A NETWORK OF 106 HOSPITALS IN EUROPE IN 26 EUROPEAN COUNTRIES.

A GREAT PROJECT IN LATIN AMERICA WITH 57 HOSPITALS WORKING ON THE LARGE-SCALE ACLARA STUDY.

19 PAPERS PUBLISHED IN 2018.
14 ORIGINALS, 3 REVIEWS AND 2 EDITORIALS.

MORE THAN 200 INVESTIGATORS WORKING ON EF CLIF SPONSORED PROJECTS SUPPORTING RESEARCH PROJECTS WITH MORE THAN 4,000,000 € / YEAR.

MEAN IF 7.68

IF > 10 11
The EF Clif organized an international meeting at the Foundation headquarters, to welcome Paolo Angeli as the new Chairman of the EASL-Clif Consortium.

Among the participants, there were most of the Steering Committee Members of the EASL-CLIF Consortium, a selected group of investigators from the PREDICT Study, the Principal Investigators of the 2018 research program of the EF Clif, members of the Grifols Chair, Dr Tom Henning Karlsen, EASL General Secretary, Professors Roger Williams and Flair Carrilho.

The meeting included two sessions: In the first one, PI’s from the EASL-CLIF Consortium and the Latin-American CLIF Consortium presented the final ongoing investigations from the CANONIC Study, the current state of the PREDICT Study and the launch of the ACLARA Study, an observational investigation starting in May 2018 assessing ACLF in 58 university hospitals from Argentina, Brazil, Chile, Colombia, Mexico, Panama, Paraguay, Peru and Mexico; and the OBSERVAH Study, a global (Europe, America and Asia) observational investigation of patients with Acute Alcoholic Hepatitis, which is planned to start in September 2018.

The second session covered the translational projects from the Grifols Chair, aimed at assessing the mechanism of systemic inflammation in acute decompensation and ACLF in cirrhosis, the immune modulatory effect of albumin, and the importance of integrated cohorts and big data in modern clinical and translational research.

After the end of the workshop, all the participants and the members of the EF Clif Staff enjoyed a dinner served by the Restaurant Gaig.

April 18th 2018

THE EASL CLIF CONSORTIUM GENERAL ASSEMBLY AND STEERING COMMITTEE WERE HELD DURING THE EASL INTERNATIONAL LIVER CONGRESS 2018 AT PARIS.

More than 80 investigators of the EASL Clif Consortium took part in the Assembly, where the speakers gave a comprehensive overview of the latest researches in the setting of EF Clif and had the opportunity to exchange experiences.

In turn, the Steering Committee meeting broadly agreed with the inclusion of 9 new research units in the Consortium, bringing to a total of 196 the number of centres in the EASL-Clif Consortium.

May 01th 2018

NEW VISITING RESEARCHER AT THE EF CLIF.

Dr Wenji Gu, medical investigator working on the group of Dr Hai Li in Shanghai, spent three months at the EF Clif central headquarters in Barcelona.

Dr Wenji Gu is a medical investigator, finishing her Master at the Department of Gastroenterology in Ren Ji Hospital, School of Medicine, and at Key Laboratory of Gastroenterology & Hepatology in Shanghai Jiao Tong University.

Her research is mainly focused on three related topics:

1. Describe the epidemiology of ACLF in China.
2. Establish diagnostic criteria for Chinese ACLF patients with HBV to determine whether there are universally accepted diagnostic criteria for both Eastern and Western types of the disease.
3. Explore the clinical course of ACLF patients, quantify the severity of the disease and establish a prognosis model for both ACLF patients and AD patients. She spent 3 months working at our Headquarters in Barcelona to extend her expertise on the ACLF, under the direction of Prof Vicente Arroyo, who helped her to finish some of her investigations initiated at the Shanghai Jiao Tong University.

These studies aim at improving early recognition of ACLF patients characterized by high short-term mortality, and eventually halting such epidemic.

Dr Gu stage pretend to be the first of many and falls within the initiatives of the EF Clif to pivot the role of the Foundation in the advancement of research in decompensated cirrhosis by strengthening ties between the international community and to enhances the collaboration between different study groups.
The principal investigators of the ACLARA study met during the annual ALEH congress.

23 PIS participated in the work session on 21st September in Punta Cana, where they shared their views and prospects on the current state of the Project.

The discussion was focused on coordinating the efforts into reaching common act policies. Headed by the PIS of the Study, Dr Flair Carrilho, Dr Vicente Arroyo and Dr Richard Moreau and with the assistance of Dr Alberto Q. Farias’ Study coordinator, the meeting was also instrumental to work further on different technical aspects and establish further guidelines of the ACLARA STUDY.

October 12th 2018

First training workshop for the participants in the ACLARA study.

The workshop was held on 1st and 2nd October 2018 at the Faculty of Medicine of the USP in Sao Paulo, with the participation of specialists from Argentina, Brazil and Chile.

The first session served as an introduction to the management of the samples, followed by a second one focused on the protocol guidelines and the use of the OII-Consoritium scores. During the second session, which lasted the whole day of October 2nd, the two working groups learnt about sample management and data introduction in the eCRF for the ACLARA Study through case studies.

November 7th 2018

The 2nd ACLARA workshop took place in the Auditorium of the Clínicas Médicas Sur Mexico City.

The workshop, which was a great success was celebrated under the patronage of Dr Misael Uribe on 30th and 31st of October 2018.

24 professionals from Brazil, Colombia, Panama, Mexico and Peru were trained in a two-days workshops, similar to the previous one held in Sao Paulo.

November 26th 2018

The ACLARA Study launched.

First inclusions in the Aclara Study.

The first inclusion week of the Aclara study finished with two patients recruited in Hospital das Clínicas de Sao Paulo University.

At the end of November, there were 17 centres ready to start inclusion. The inclusion rate has grown apace, reaching 63 patients by the end of 2018.
THE CLIF CONSORTIUM HOSPITAL NETWORK & ASSOCIATED INVESTIGATORS

HÔPITAL HENRI MONDOR
Christophe Duvoux
HÔPITAL CLAUDE HURIEZ
Philippe Mathurin
HÔPITAL TENON – PARIS
Jean Didier Grange
HÔPITAL PITÉ SALPETRİÈRE – PARIS
Dominique Thabut
RENNE UNIVERSITY HOSPITAL
Pierre Bisrot
CHU TOULOUSE
Christophe Bureau
Jean-Marie Peron
HÔPITAL PAUL BROUSSE
Faouzi Saliba
Audrey Colly
Eric Laevaque
Didier Samuel
GEORGIAN NATIONAL HEPATOBILIARY CENTER
V Katsarava
Gocha Barbakadze
AACHEN UNIVERSITY HOSPITAL
Christian Trautwein
Pavel Strnad
UNIVERSITY OF BONN
Jonel Trebicka
Frank Lammert
HAMBURG-EPPENDORF UNIVERSITY HOSPITAL
Dieter Häussinger
UNIVERSITY HOSPITAL OF ESSEN
Guido Garken
IW COETZEE UNIVERSITY HOSPITAL FRANKFURT
Stefan Zouzem
George Dutz
Christian Lange
Ole Kristian Weidmann
Martin-Walter Walker
Tanja Wieland
UNIVERSITY HOSPITAL OF FREIBURG
Robert Thimme
UNIVERSITY HOSPITAL VALE-LE-WITTEMBERG
Alexander Zippich
HAMBURG-EPPENDORF UNIVERSITY HOSPITAL
Ansgar Lohse
Valentin Fuhrmann
Daniel Barten
HANOVER MEDICAL SCHOOL
Thomas von Haehn
Michael Manns
UNIVERSITY HOSPITAL OF HEIDELBERG
Wolfgang Schimmel
Uta Marle
UNIVERSITY HOSPITAL OF HAMBURG
Frank Lammert
JENA UNIVERSITY HOSPITAL
Tony Bruns
UNIVERSITY HOSPITAL LEIPZIG
Cornelius Engelmann
UNIVERSITY OF MAINZ HOSPITAL
Peter R. Galle
Marcus-A. Wörns
MUNICH UNIVERSITY HOSPITAL
Alexander Garbes
Cosmin Hopf
MÜNSTER UNIVERSITY HOSPITAL
Hartmut Schmidt
UNIVERSITY HOSPITAL OF MAGDEBURG
Ali Canbay
UNIVERSITY HOSPITAL WÜRZBURG
Andreas Gaier
UNIVERSITY OF DEBRECEN
Mária Papp
ICELAND
11
IRELAND
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ITALY
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LATVIA
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LITHUANIA
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NETHERLANDS
16
NORWAY
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POLAND
18
PORTUGAL
19
ICELAND
11
LANDHAUS UNIVERSITY HOSPITAL
Sigurdur Olafsson
ST VINCENT’S UNIVERSITY HOSPITAL
Aiden McCormick
Jun Liang Chia
ALMA-MATER STUDIORUM
MAURO BERNARDI
PAOLO CARACCINI
MARCO DOMENICIANI
Filippo Morandi
Giacomo Zaccherini
ASL BIRINDI
PIETRO GATTI
OSPEDALE NAZIUNALE, MILANO
Luca Saverio Belli
POLICLINICO SAN DONATO
Francesco Salerno
AZIENDA OSPEDALIERA DI PADOVA
Paolo Angel
Elisabetta Gola
Carlo Marzol
Sara Montagnese
Salvatore Piano
Antonietta Romano
POLICLINICO DI PALERMO
Vito di Marco
UNIVERSITY HOSPITAL OF MESSINA
Giovanni Raimondo
UNIVERSITY OF ROME
Manuela Merli
Omero Pigion
AZIENDA OSPEDALIERA CITTÀ DELLE SAPIENZE
Salve Carlo Antonio
HOSPITAL SANTA MARIA. FACULADE DE MEDICINA DA UNIVERSIDADE DE LISBOA
José Velosa
CENTRO HOSPITALAR DO PORTO
Filipe Nery
LIGHT NIGHTS HOSPITAL
José A Presa Ramos
CENTRO CÂMBRICO HOSPITAL
Filipe S. Cardoso
ITALY
13
INTERNAL MEDICINE UNIVERSITY OF UDINE
Pierluigi Toniutto
SIAULIAI HOSPITAL
Gitana Acute
LEIDEN UNIVERSITY MEDICAL CENTER
Minneke J. Coenraad
ERASMUS UNIVERSITY MEDICAL CENTER ROTTERDAM
Rob de Man
OSLO UNIVERSITY HOSPITAL
Zhigang Komsopki
MEDICAL UNIVERSITY OF WARSAW
Marcin Krawczyk
POMERIAN MEDICAL UNIVERSITY
Anna Borón Kaczmarska
CENTRO HOSPITALAR DO PORTO
Filipe Nery
HUNGARY
10
22
23
EXTERNAL COLLABORATORS

Claudia Alves Couto
Hospital das Clínicas. Federal University of Minas Gerais (Belo Horizonte, Brazil)

Marco Arrese
Pontifical Catholic University of Chile (Santiago, Chile)

Flair Arratia
Hospital de Clínicas. São Paulo (Brazil)

Raúl Castro
Hospital Edgardo Rebagliati (Lima, Peru)

André Castro Lyra
Hospital de Clínicas. São Paulo (Brazil)

Luis Colombato
Hospital Británico (Buenos Aires, Argentina)

Shilpa Chokshi
Foundation for Liver Research (London, UK)

Milagros Dávalos Moscol
Hospital Edgardo Rebagliati (Lima, Peru)

Giovanni Faría Silva
Faculty of Medicine of Botucatu, UNESP (Brazil)

Fernanda Fernandes Souza
Hospital das Clínicas. Ribeirão Preto Medical School (Brazil)

Daniel Ferraz de Campos Mazo
University of Campinas School of Medical Sciences (Brazil)

Adrián Gadano
Hospital Italiano (Buenos Aires, Argentina)

David Gómez-Cabrero
University of Navarra (Pamplona, Spain)

Maria Sarai González Huezo
ISSEMyM Medical Center (Toluca, Mexico)

Cristophe Junot
CEA (Gif-sur-Yvette, France)

Paulo Lisboa Bittencourt
Hospital Português in Salvador (Brazil)

Mario Reis Alvares da Silva
Hospital das Clínicas. Porto Alegre (Brazil)

Juan Pablo Roblero
Clinical Hospital San Borja Ariasán (Santiago, Chile)

Liliana Sampán Costa Mendes
Base Hospital of the Federal District (Brasilia, Brazil)

Tarsicio dos Santos da Rocha
University Hospital Walter Cantídio (Fortaleza, Brazil)

Gustavo Santos Pereira
Federal Hospital of Bonferruca (Rio de Janeiro, Brazil)

Carlos Terra
University Hospital Pedro Ernesto (Rio de Janeiro, Brazil)

Claudio Toledo
University of Chile, Valdivia Hospital (Santiago, Chile)

Aldo Torre
National Institute of Medical Sciences and Nutrition Salvador Zubirán (Mexico City, Mexico)

Misael Uribe
Clinica Foundation Médica Sur (Mexico City, Mexico)

Ângelo Zambam de Mattos
Santa Casa de Misericordia Hospital (Porto Alegre, Brazil)
11. IMPACT FACTOR

SCIENTIFIC MAGAZINES

- A. Journal of hepatology
- B. Hepatology
- C. The American Journal of Gastroenterology
- D. Clinical Gastroenterology and Hepatology
- E. British Journal of Pharmacology
- F. Critical Care Medicine
- G. Journal of Leukocyte Biology
- H. Expert Review of Gastroenterology and Hepatology
- I. Canadian Journal of Gastroenterology and Hepatology
- J. Visceral Medicine

PAPERS

- A. Q1/ID
- B. Q1/ID
- C. Q1/ID
- D. Q1/ID
- E. Q1/ID
- F. Q1/ID
- G. Q1/ID
- H. Q1/ID
- I. Q1/ID
- J. Q1/ID

SUMMARY OF ACTIVITIES 2018

IF > 10 TOTAL MEAN

- IF: 7.68
- TOTAL PAPERS: 11
- OTHERS: 19
- Q1: 72%
- Q2: 6%
- Q3: 22%
12. PROGRESS REPORT


The scientific outcome in 2018 has consisted of 19 published articles:
Coagulation failure in patients with acute-on-chronic liver failure and decompenated cirrhosis: beyond the international normalized ratio.

Hepatology 2018; 68: 2325-2337

The aim of the study was to characterize the coagulation profile in 24 patients with acute decompensation (AD) and 38 patients with acute-on-chronic liver failure (ACLF) and its relationship with systemic inflammation, transfusion requirements, bleeding events and short-term survival. Blood samples for thromboelastometry were obtained at admission and 72 hours thereafter. Patients with ACLF showed more hypocoagulable characteristics than patients with AD (prolonged time to initial fibrin formation and clot formation and decreased maximum clot firmness and α-angle values) and higher prevalence of hypocoagulable profile (61% versus 16%). Hypocoagulability was associated with systemic inflammation and higher short-term mortality rate (45% vs 16%) but not with bleeding or transfusion requirements.


The concentration of both biomarkers increased with increasing severity of AD and ACLF. Close correlation existed between cell death markers and makers of systemic inflammation, respectively. The expression of both markers in plasma was significantly higher in patients with decompenated cirrhosis (n= 256) and of healthy subjects. Caspase-cleaved keratin 18 (cK18) and keratin 18, which reflect apoptotic and total cell death, respectively, were measured in plasma. The concentration of both biomarkers increased with increasing severity of AD and ACLF. Close correlation existed between cell death markers and markers of systemic inflammation, respectively. The expression of both markers in plasma was significantly higher in patients with decompenated cirrhosis (n= 256) and of healthy subjects.

The plasma levels of oxidized albumin forms (HANA and HNA2) were significantly increased in patients with decompenated cirrhosis (n= 256) included in the Canonic study with respect to healthy subjects (2= 48) and both forms increased gradually in the former group of patients in parallel with systemic inflammation (as estimated by the plasma levels of IL-6, IL-1β, TNF and IL-8) and disease severity (from compensated cirrhosis to patients with decompenated cirrhosis and with acute-on-chronic liver failure). To explore the ability of oxidized albumin to induce systemic inflammation by triggering the activation of circulating leukocytes, we prepared these oxidized albumin forms ex vivo and their posttranslational modifications monitored by liquid chromatography-quadrupole time-of-flight/mass spectrometry. HNA1 but not HNA2 increased IL-6, IL-1β, TNF-α and mRNAs and protein expression in leukocytes from both healthy subjects and patients with cirrhosis. Moreover, HNA1 upregulated the expression of anti-inflammatory enzymes and the production of inflammatory eicosanoids (PGE2, PGF2α, thromboxane B2 and leukotriene B4). Kinome analysis of peripheral revealed that HNA1 induced the phosphorylation of p38 mitogen-activated protein kinase. In conclusion, HNA1 triggers and inflammatory response in peripheral blood mononuclear cells providing a rationale for its removal and replacement by reduced albumin in the prevention of systemic inflammation in patients with advanced cirrhosis.

15. FINANCIAL REPORT