



2023
SCSG
LIVER SYMPOSIUM
DECEMBER 9-10, 2023



1st Vinay Sundaram Memorial Lecture, SCSG 2023

Acute on Chronic Liver Failure Focus on Role of Liver Transplantation

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Consultant, Royal Free Hospital
Scientific Director, EFCLIF



UCL

NHS

Royal Free London
NHS Foundation Trust

Disclosures

Founder: Yaqrit Ltd., Hepyx Ltd., Cyberliver Ltd, Gigabiome

Inventor: Ornithine Phenylacetate; DIALIVE, CARBALIVE, G-TAK, CirrhoCare, Alcochange

Speaker and Grant Reviewer: Grifols

Research Collaborator: Yaqrit Ltd.

The Vinay Sundaram Legacy (1978–2022)



Set the scene for defining role of liver transplantation in ACLF

- Does liver transplantation for ACLF-3 result in transplant benefit?
- Should patients with ACLF-3 be prioritized on the liver transplantation waiting list?
- Timing of liver transplantation vs. use of marginal organs?
- When is a liver transplant futile in patients with ACLF-3?
- The cost of transplanting ACLF-3 patients

ACLF and Liver Transplantation

- The Problem
- Role of Liver Transplantation: The knowns and the unknowns
 - Are the current allocation systems appropriate for ACLF?
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 - Predictors of poor LT outcome
 - Timing vs Severity of ACLF vs Marginal organ usage
 - Factors associated with potential futility
- UK experience of a pilot of a new allocation system
- CHANCE study



ACLF and Liver Transplantation

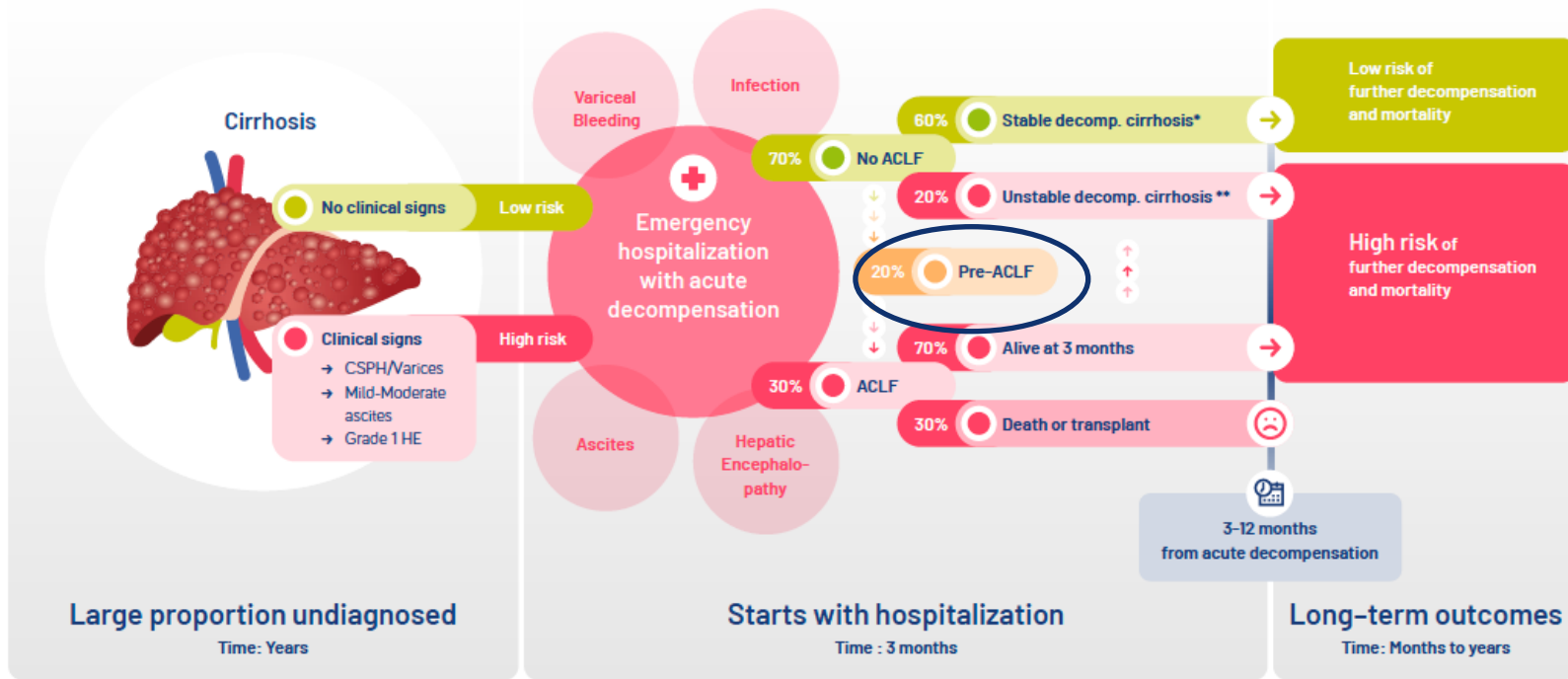
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AV, 35yr M, PSC Cirrhosis / UC, Bowel Resection; Sepsis; ICU

- Week 1: Progressive Jaundice following cholangitis (Bili 322)
 - 3 previous hospitalization for sepsis
- Week 2: Renal Failure; CRRT; Inotropes
- Week 3-4: Hepatic Encephalopathy (Grade 3)
- *Listed for LT: Receives organ after 6-days (appeal)*
- *Weeks 5-12: Multiorgan Support*
- *Weeks 12-60: Rehabilitation*
 - *Return to work*

Trajectory of Cirrhosis



* Stable Decomp Cirrhosis: 100% Survival over 3-months ** Unstable Decomp Cirrhosis: 70% Survival over 3-months *** pre ACLF: 50% Survival over 3-months
CSPH: Clinically significant portal hypertension

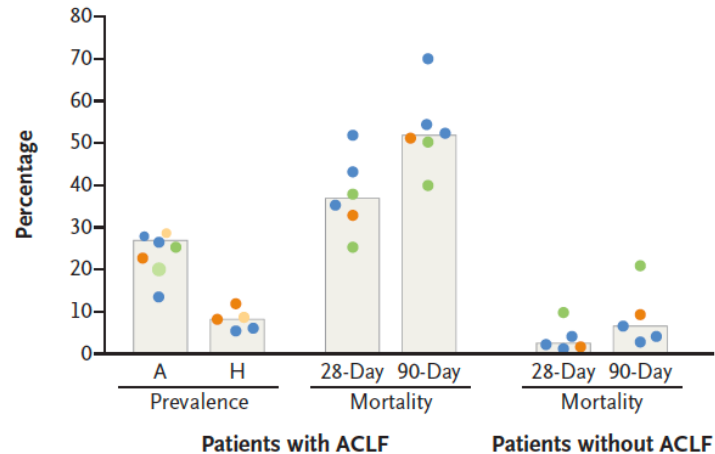
Diagnostic criteria of ACLF and its validation

Diagnostic criteria of organ disfunction and failure

Organ System	1 point	2 points	3 points
Liver	Bilirubin <6 mg/dL	Bilirubin 6-11.9 mg/dL	Bilirubin ≥12 mg/dL
Kidney	Creatinine <1.5 mg/dL	Creatinine 2-3.4 mg/dL	Creatinine ≥3.5 mg/dL or RRT
	Creatinine 1.5-1.9 mg/dL		
Brain (West Haven Score)	Grade 0	Grade 1-2	Grade 3-4
Coagulation	INR <2.0	INR 2.0-2.4	INR ≥2.5
Circulation	MAP ≥70 mmHg	MAP <70 mmHg	Vasopressor requirement
Respiratory	PaO ₂ /FiO ₂ >300	PaO ₂ /FiO ₂ 201-300	PaO ₂ /FiO ₂ ≤200
	SpO ₂ /FiO ₂ >357	SpO ₂ /FiO ₂ 215-357	SpO ₂ /FiO ₂ ≤214

Diagnostic criteria of ACLF and ACLF grades

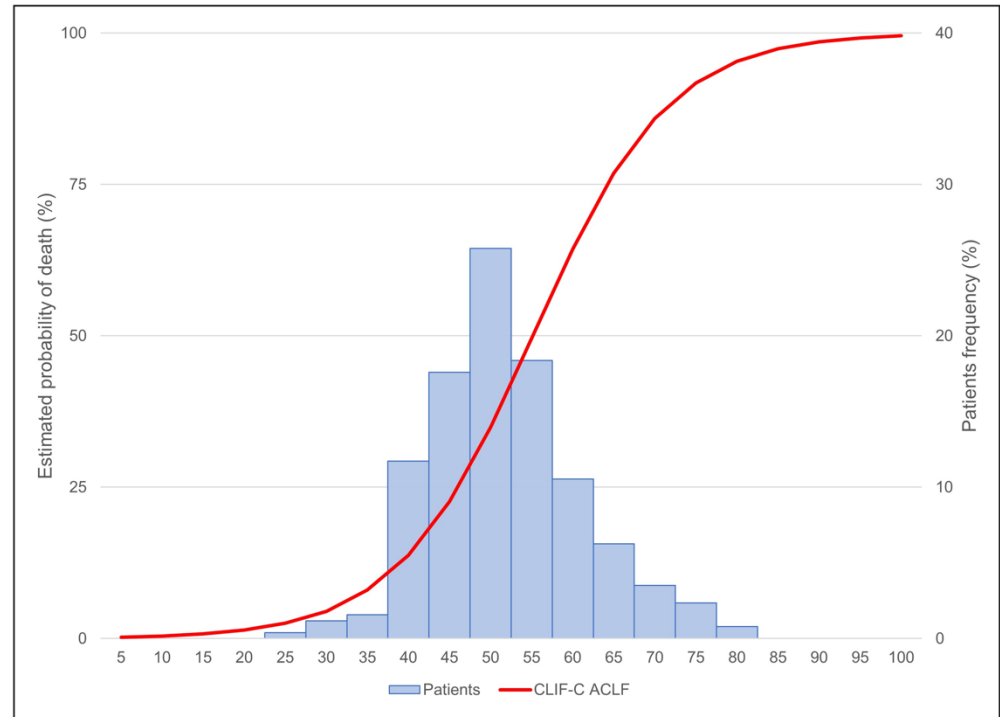
Patients group	Prevalence over 1287 patients (%)	28-day Mortality (%)	Assigned category
Absence of OF	68.3	4.4	Absence of ACLF
Single non Kidney OF without KD or BD	9.9	6.3	
Single KF	6.7	18.6	ACLF-1
Single non Kidney OF with KD or BD	4.2	27.8	ACLF-1
Two OFs	7.5	32.0	ACLF-2
Three OFs	1.9	68.0	ACLF-3
Four to six OFs	1.4	88.9	ACLF-3



- **Europe: CANONIC and PREDICT (n=1343; n=1375);**
- **Asia: Li et al. (n=890), KACLIF (n=1235 patients), COSSH (n=1031)**
- **USA: Mahmud et al. (n=80,383 patients) and Hernaez et al. (n=72,316)**
- **Latin America: ACLARA (n=1077)**

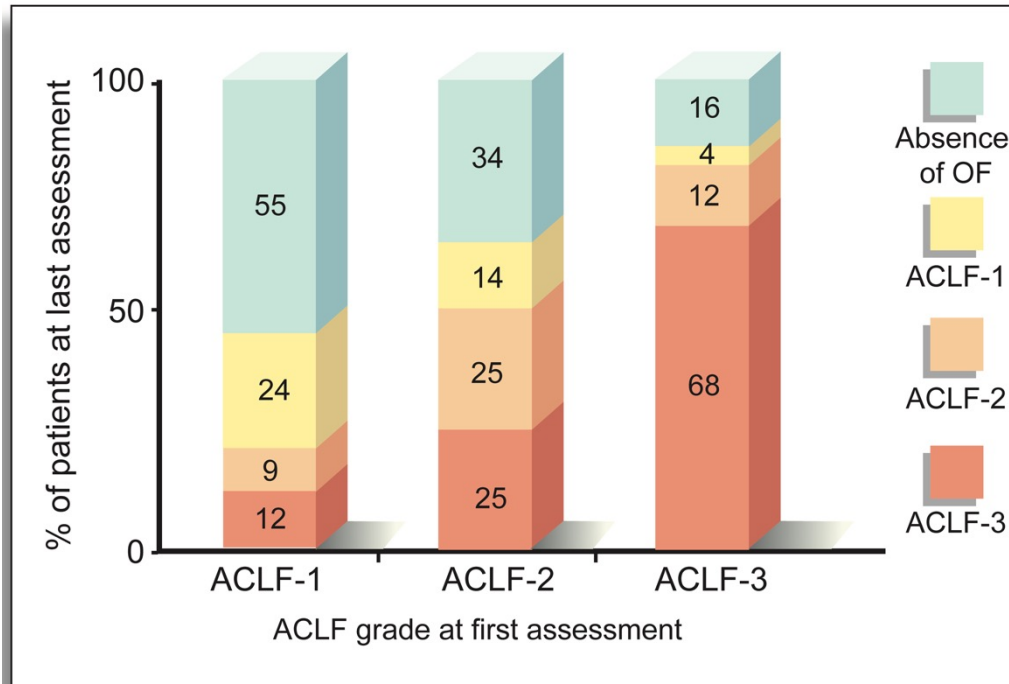
Prognostic Model of ACLF: The CLIF-C ACLF Score

- New model – CLIF-C ACLF score
 - CLIF-OFs
 - Age + WBC
 - Result: 0-100
 - Predicts 28d mortality
- $\leq 45 = 20\%$
- **Our patient in week 2: 70 (90% 28-day mortality)**
- Performs better than MELD-Na and Child-Pugh in predicting mortality
- Validated in 11 studies world-wide



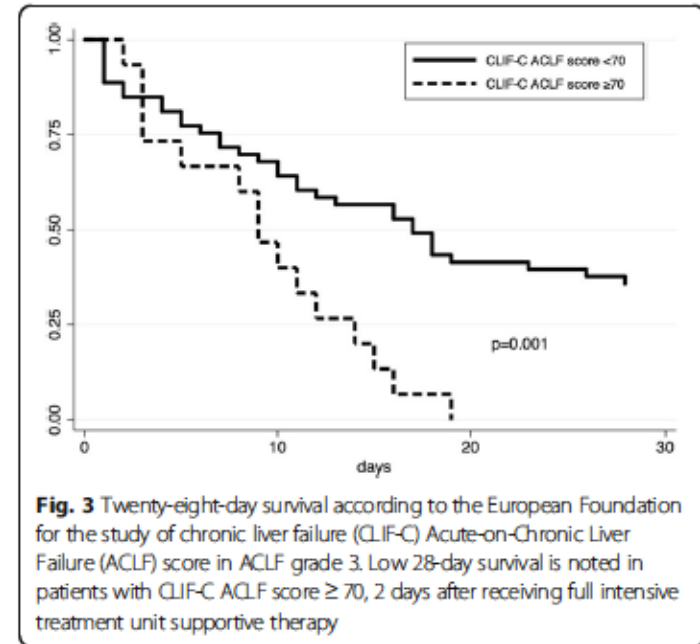
ACLF Is Potentially Reversible and Dynamic

Clinical course of ACLF



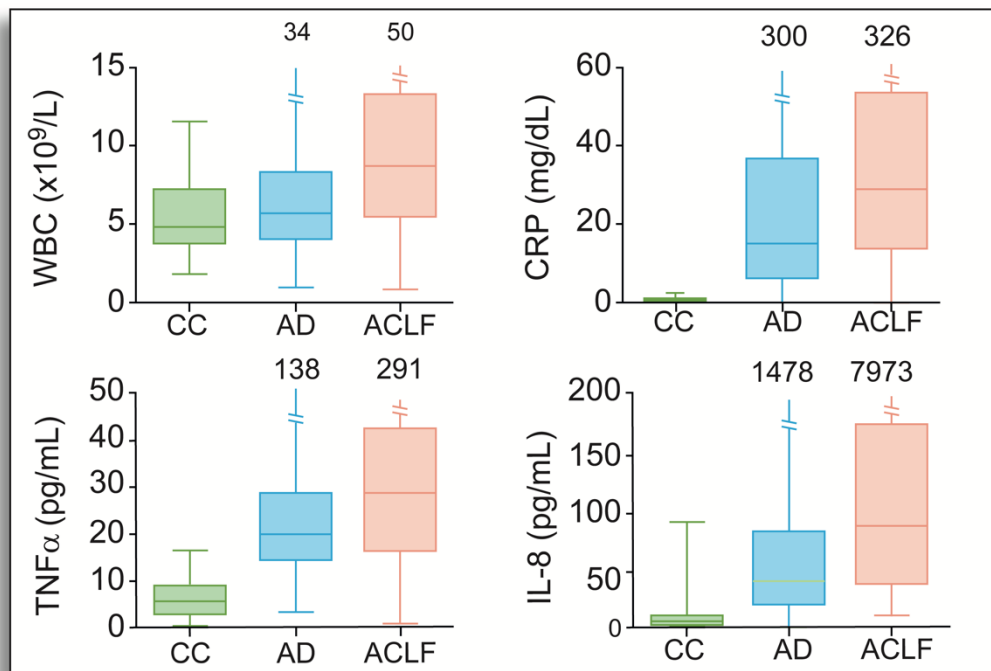
When Is Ongoing ICU Care Futile

Patients group	Prevalence over 1287 patients (%)	28-day Mortality (%)	Assigned category
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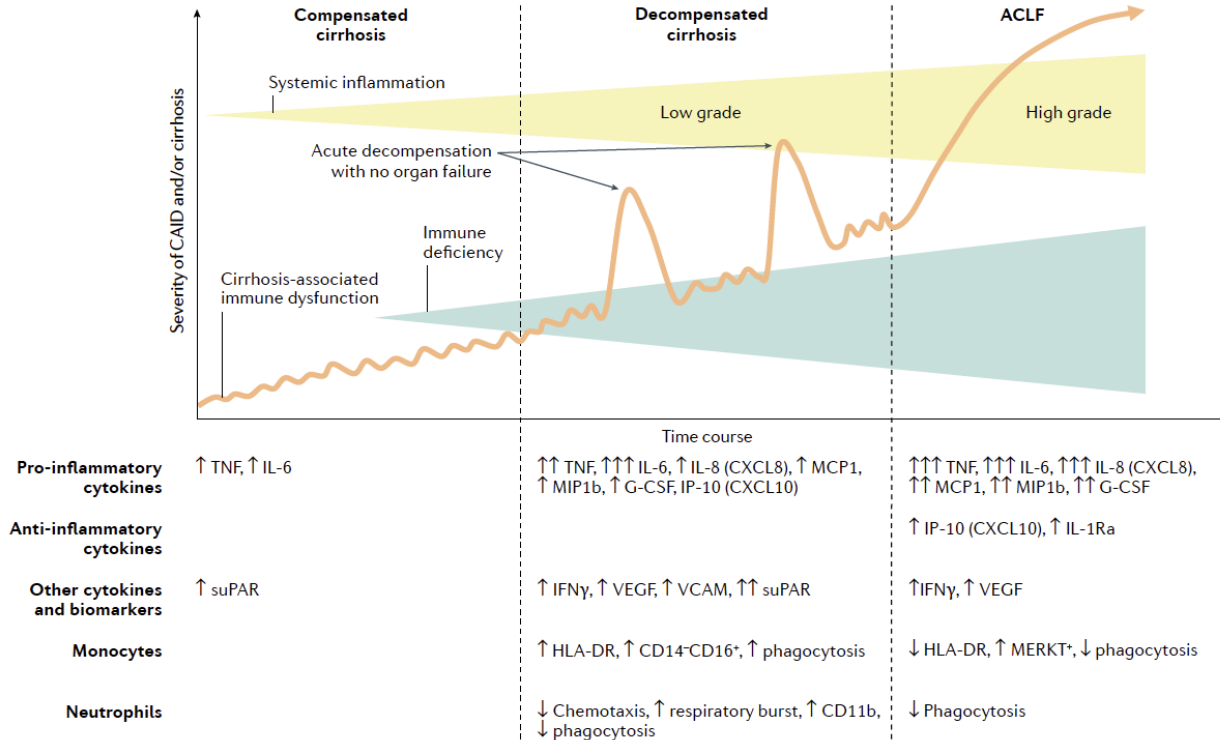
Inflammation Is the Underlying Mechanism

Inflammatory markers

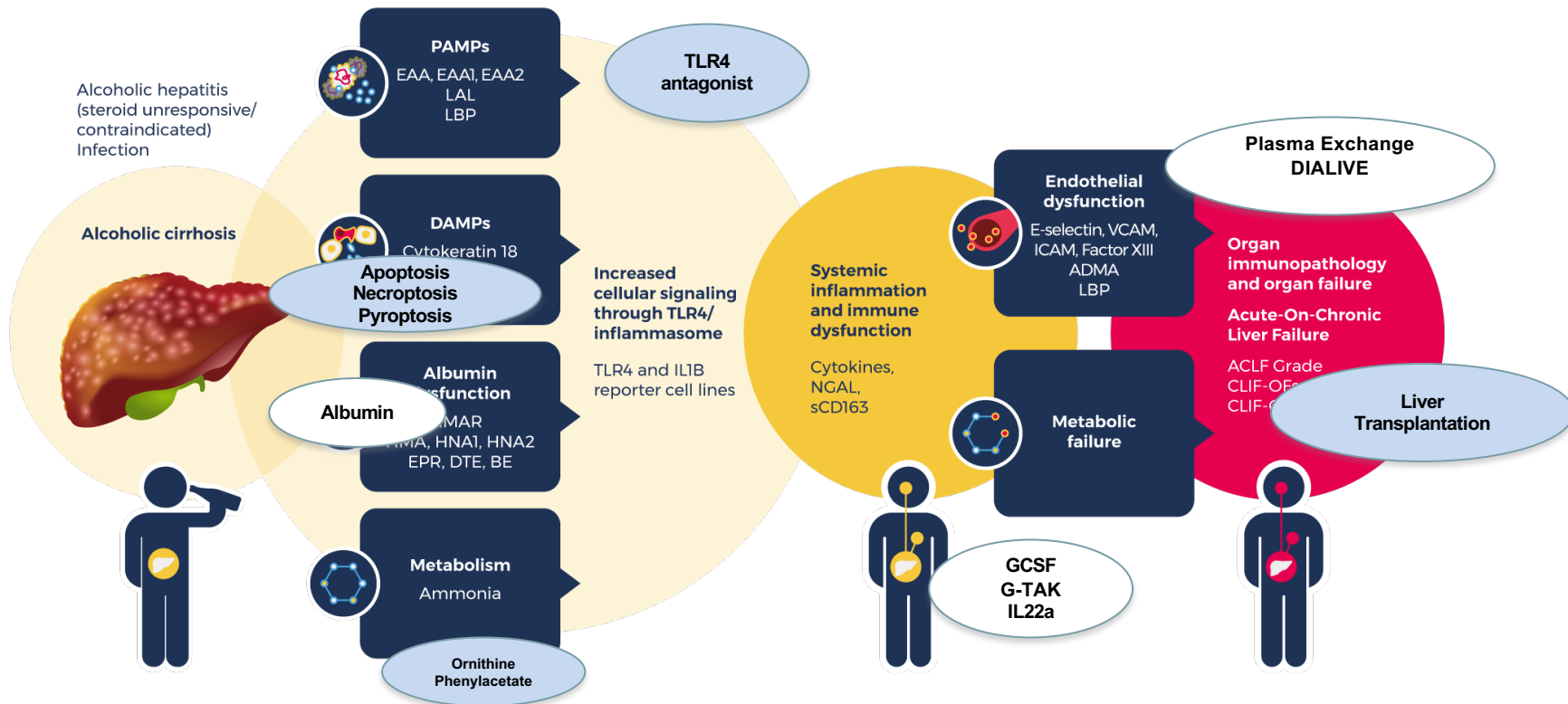


Cirrhosis-associated immune dysfunction

Agustín Albillos^{1,2,3}, Rosa Martín-Mateos^{1,2,3}, Schalk Van der Merwe^{4,5},
Reiner Wiest⁶, Rajiv Jalan⁷ and Melchor Álvarez-Mon^{2,3,8}



New Therapies Under Development



ACLF and Liver Transplantation

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MELD-Na Underestimates the Risk of Death of ACLF Patients on the Waiting List

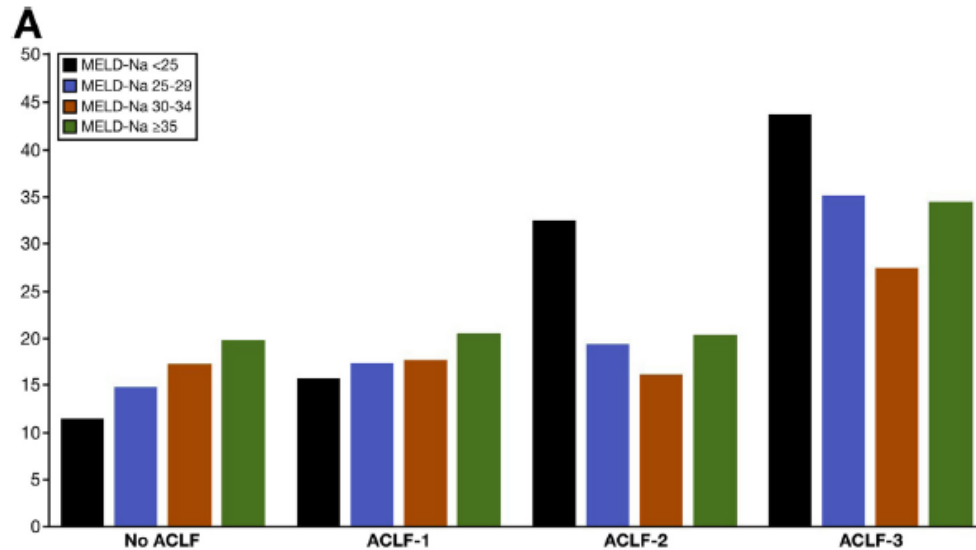
UNOS database: 2005-2016

ACLF 0: 79,520



ACLF 1: 9640

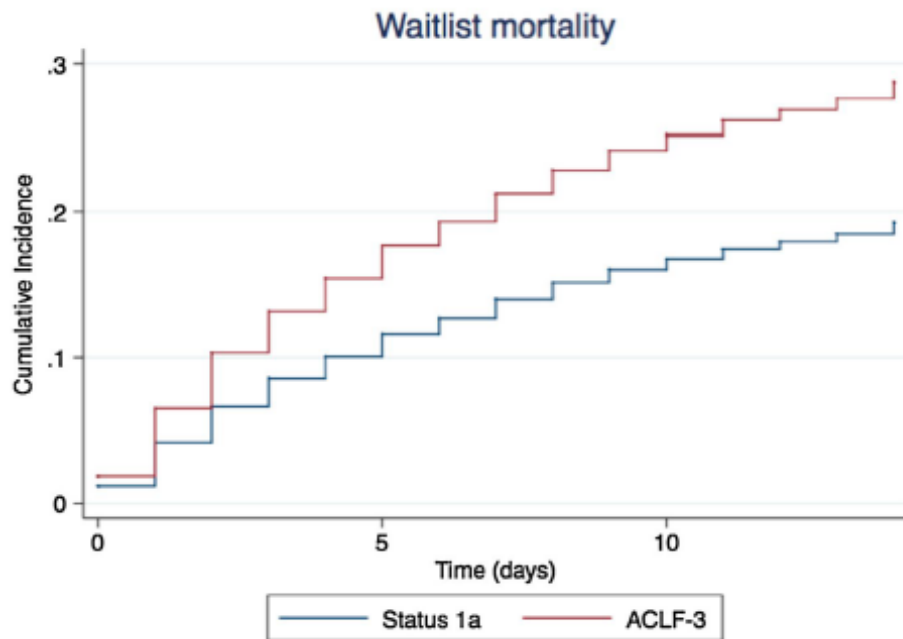
ACLF 2: 6079

ACLF 3: 5355



Patients With Acute on Chronic Liver Failure Grade 3 Have Greater 14-Day Waitlist Mortality Than Status-1a Patients

Vinay Sundaram,¹ Parth Shah,¹ Robert J. Wong ², Constantine J. Karvellas ³, Brett E. Fortune,⁴ Nadim Mahmud,⁵ Alexander Kuo,¹ and Rajiv Jalan⁶



UNOS Data: 2002-2014

Status 1a: n=3377

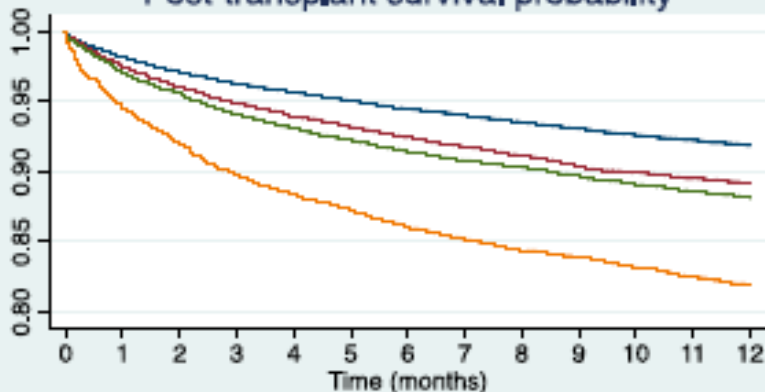
ACLF-3: n=5099

Factors Associated with Survival of Patients With Severe Acute-On-Chronic Liver Failure Before and After Liver Transplantation



Vinay Sundaram,^{1,*} Rajiv Jalan,^{2,*} Tiffany Wu,³ Michael L. Volk,⁴ Sumeet K. Asrani,⁵ Andrew S. Klein,⁶ and Robert J. Wong⁷

Post-transplant survival probability



Number at risk	0	1	2	3	4	5	6	7	8	9	10	11	12
txaclfcat = 029005	26065	24820	23430	22323									
txaclfcat = 1 7315	6563	6207	5834	5513									
txaclfcat = 2 7430	6572	6173	5746	5376									
txaclfcat = 3 6272	5287	4918	4533	4187									



UNOS database: 2005-2016

ACLF 0: 29,283

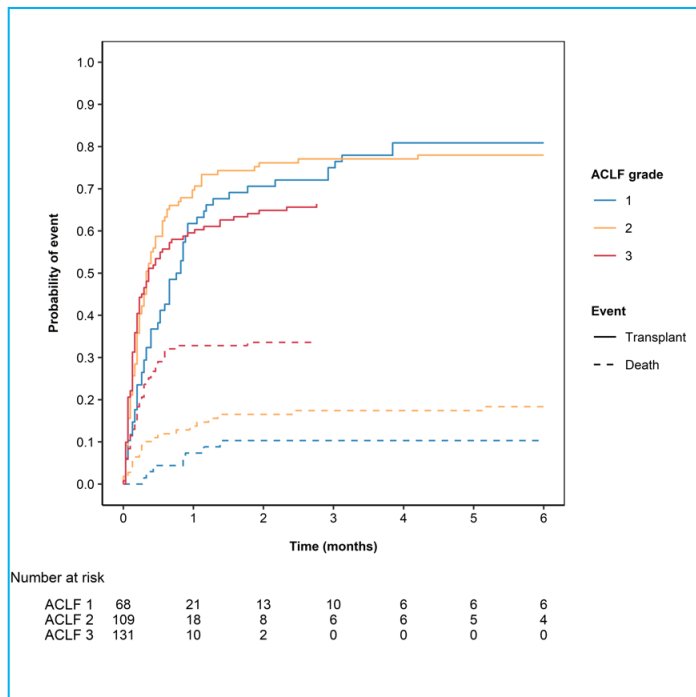
ACLF 1: 7375

ACLF 2: 7513

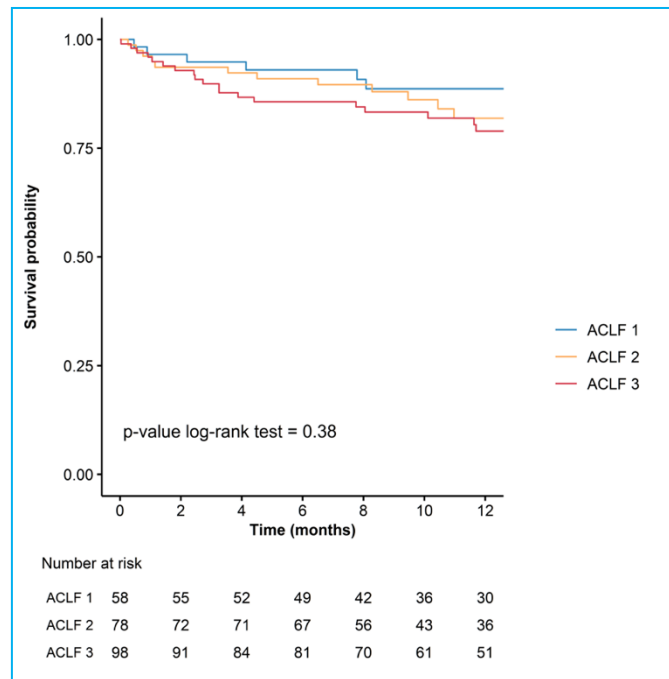
ACLF 3: 6381

Mortality on Waiting List and Post LT Survival

Probability of transplant or death using Competing risk analysis

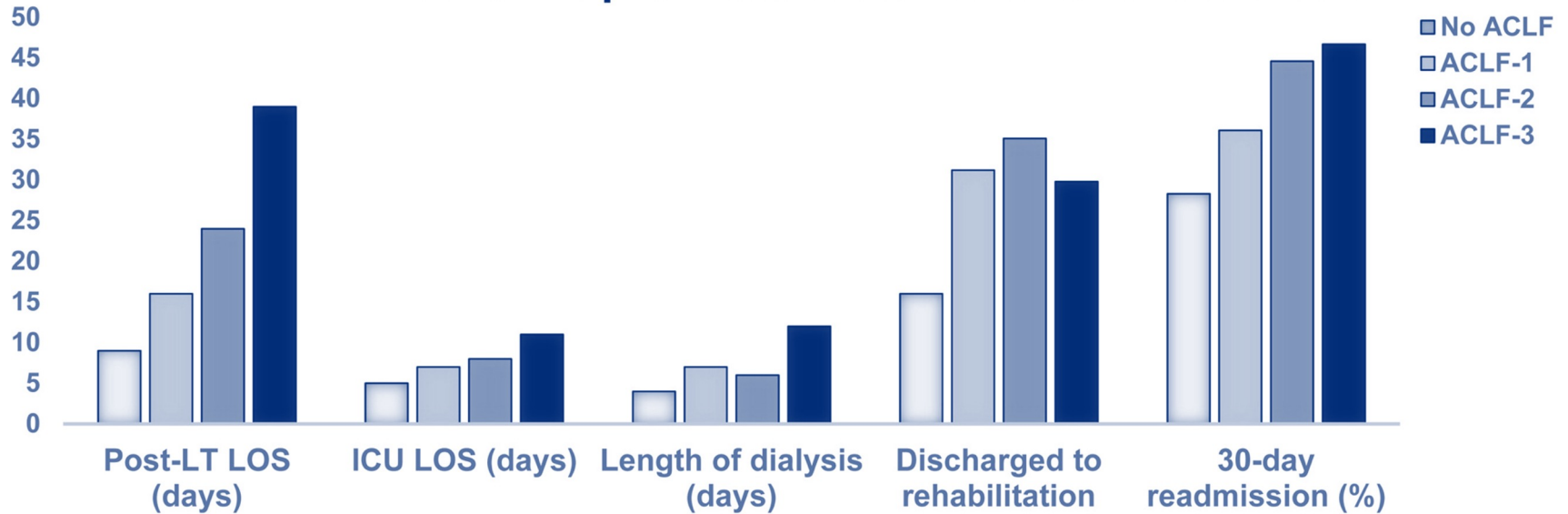


Post LT Survival

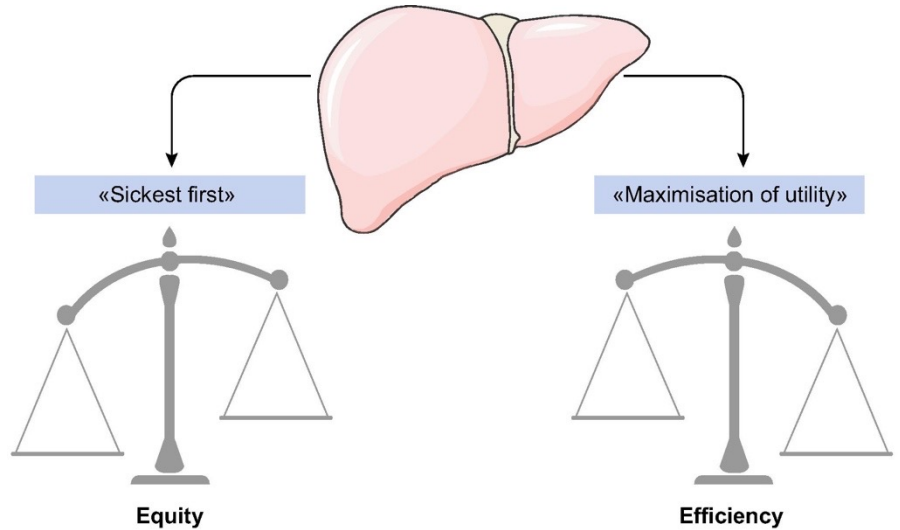


Transplanting Patients With ACLF Comes at a Cost

Post-transplant healthcare resource utilization



Timing and Implications for Organ Allocation in the MELD Era

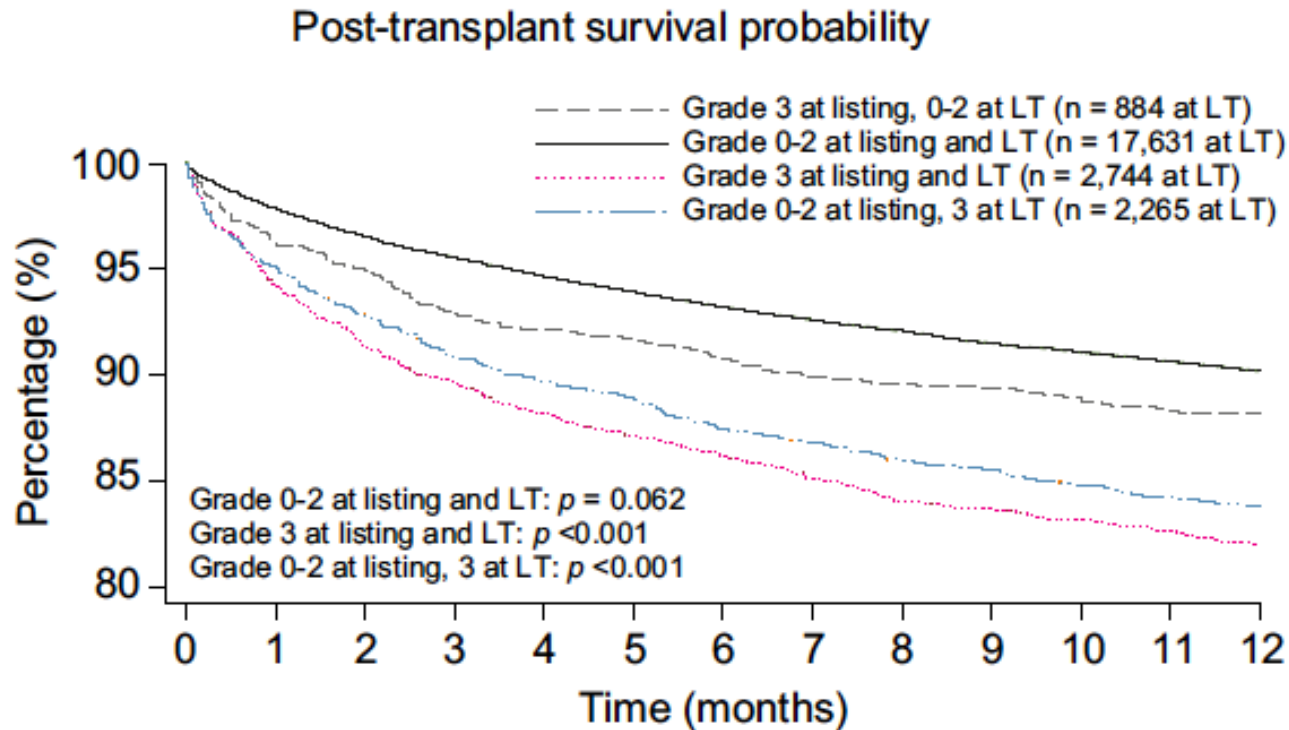


Trying to save **every patient** even with low probability of survival or very low quality of life after LT

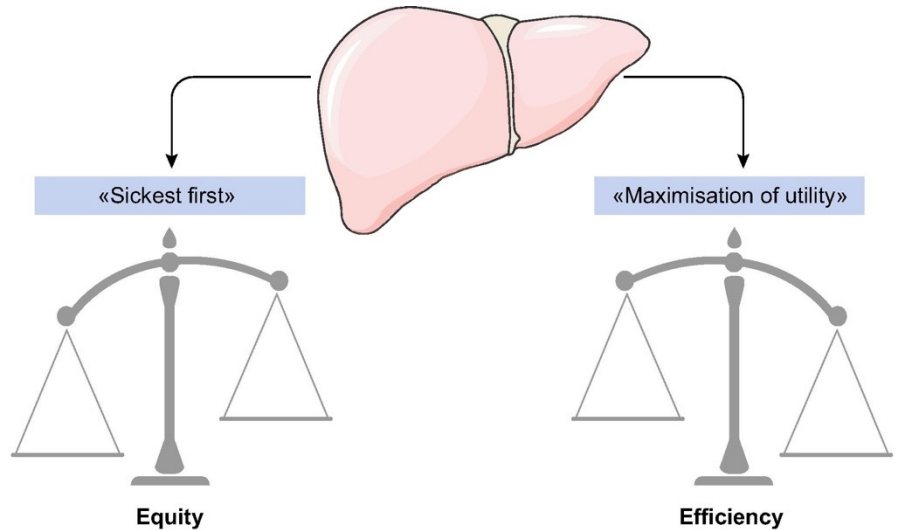
Trying to save **as many patients** in need of an LT («nameless faces») with good quality of life after LT

What is the impact of the course of ACLF on post LT-outcomes?

Optimal Timing Is Crucial as the Change in Severity of ACLF Impacts on Post LT Survival



Timing and Implications for Organ Allocation in the MELD Era

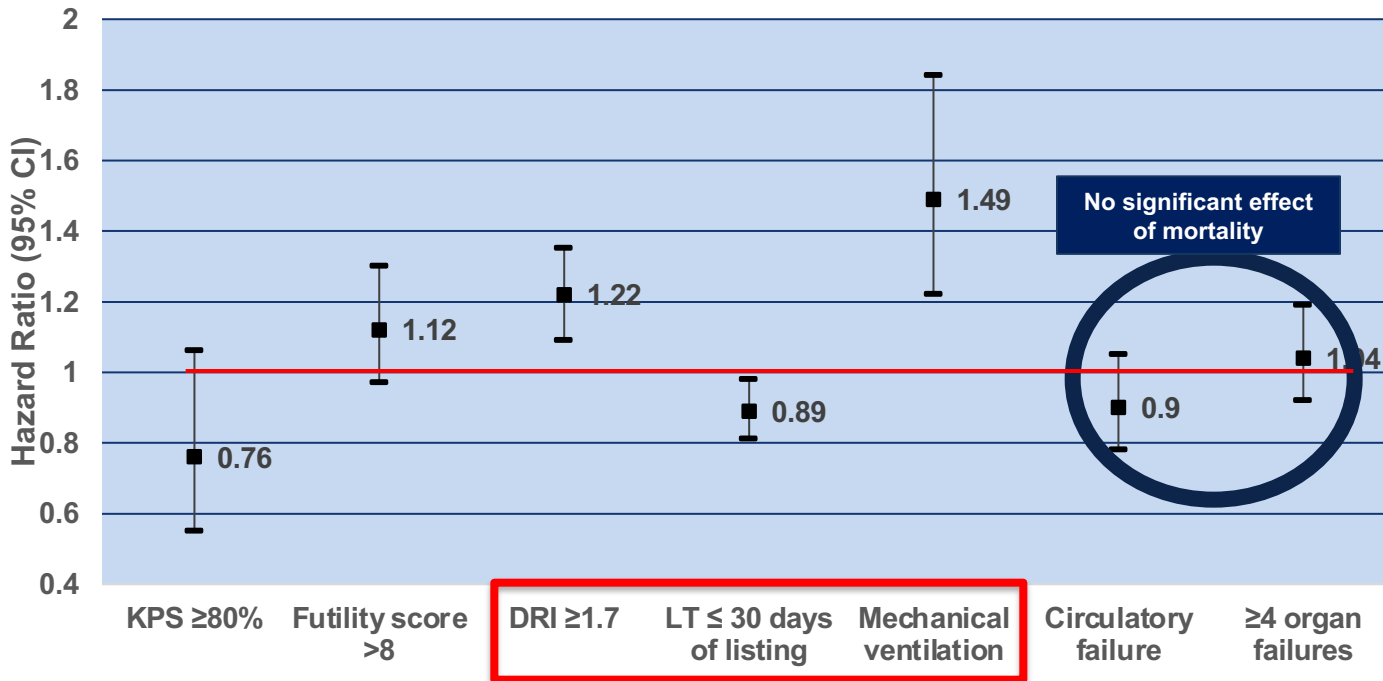


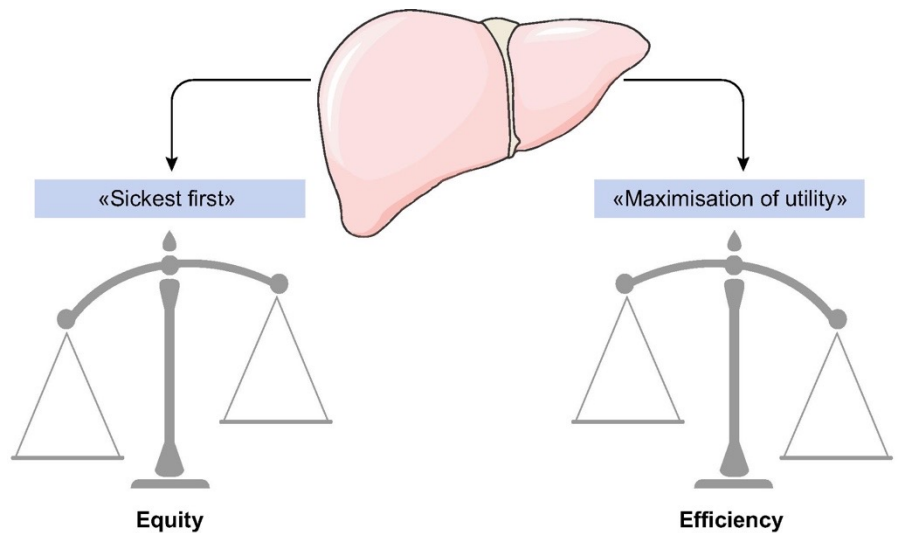
Trying to save **every patient** even with low probability of survival or very low quality of life after LT

Trying to save **as many patients** in need of an LT («nameless faces») with good quality of life after LT

Independent factors associated with a risk of death following LT

Risk Factors Associated With One-Year Post-LT Mortality





Trying to save **every patient** even with low probability of survival or very low quality of life after LT

Trying to save **as many patients** in need of an LT («nameless faces») with good quality of life after LT

The dilemma of timing vs using marginal organs to transplant ACLF patients?

Developing a Markov Model for Decision Making in High-Risk Patients

Aims

Markov decision process model to determine the optimal timing with 7 days of listing, to maximize 1-year post-LT survival, accounting for

- Organ failure recovery and
- Use of a marginal quality organ

Results

- In all patient groups, earlier transplantation yielded the highest survival benefit even when accounting for donor organ quality
- Less flexibility to decline organs among patients above age 60 or with 4-6 organ failures, due to high non-transplant survival
- This MDP model can guide in the decision to accept or decline an organ

Risk Factors High Mortality After Liver Transplantation in Severe ACLF



Severe comorbidities



Infection
(Uncontrolled/fungal/
multidrug resistant)

<150

ARDS
(PaO₂/FiO₂ ratio <150)



Time on the waiting list

>1
mcg/kg/min

High vasopressor
(Norepinephrine dose
>1 mcg/kg/min)



Transplantation using
marginal organs

>9
mmol/L

Severe lactatemia
(>9 mmol/L)

Sundaram ACLF Liver Transplantation Score (SALT-M Score and SALT-LoS Score)

MODEL Consortium
(development/internal validation)



15 Liver Transplant Centers,
521 patients with ACLF 2-3

External
validation



Strasbourg and Villejuif,
120 patients with ACLF-3

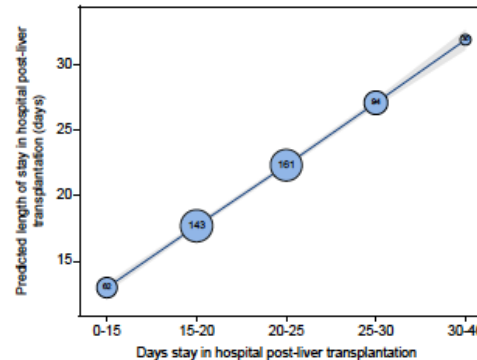
Tool: logistic regression using clinically meaningful variable selection in addition to modern selection techniques. Adequate power for 5 predictors. Used median regression to estimate median length of stay using the same principles.

- ✓ Age 50+
- ✓ Diabetes mellitus
- ✓ Body mass index (continuous)
- ✓ Circulatory failure (one or 2+ inotropes)
- ✓ Respiratory failure

Sundaram ACLF-LT (SALT)-Mortality score
predicts 1-year mortality probability post-LT

AUROC 0.72 (development)
AUROC 0.80 (external validation)

Able to assess median length-of-stay
in days post LT



Adjusted for age, body mass index, diabetes use of inotropes, respiratory failure, prior history of MDRB, RRT and WBC at LT



ACLF 2/3 & LT candidate?

→ The Sundaram score can help in the discussions of LT in these patients

MDRB, multidrug resistant bacteria; RRT, renal replacement therapy; WBC, white blood cell count

Many Unanswered Questions

- Lack of intention-to-treat results from the time of wait listing
- Detailed information about waiting list outcomes
- Best organ allocation system for this specific population
- Objective limits to define futile LT
- Ideal timing
- Characteristics of donor organ to ensure acceptable post-LT outcomes
- Long-term post-LT survival rates and impact on the quality of life (QoL)
- Resource utilization of performing LT and
- The overall results across the different continents



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- **CHANCE study**
- UK experience of a pilot of a new allocation system



CHANCE Study Design – Objectives

Primary objective



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 and transplant-free survival of patients with ACLF 2 or 3 not listed for LT.

Secondary objectives

- To assess the proportion of patients with ACLF who are listed
- To evaluate the outcomes of WL patients with or without ACLF
- To define independent predictive factors of death/delisting on the WL and develop new prognostic model and define futility criteria
- To compare characteristics of accepted grafts for patients listed with and without ACLF
- To compare post-LT quality of life in patients with and without ACLF
- To assess the costs of care in patients listed for LT with and without ACLF

CHANCE Study Design – Objectives (Contd.)



Blood, circulating cells and fluids

- Serum, plasma
- Tempus
- Buffy-coat
- PBMCs
- Urine, saliva



Tissues

Biopsy from liver of recipient

- Histology
- Protein, RNA



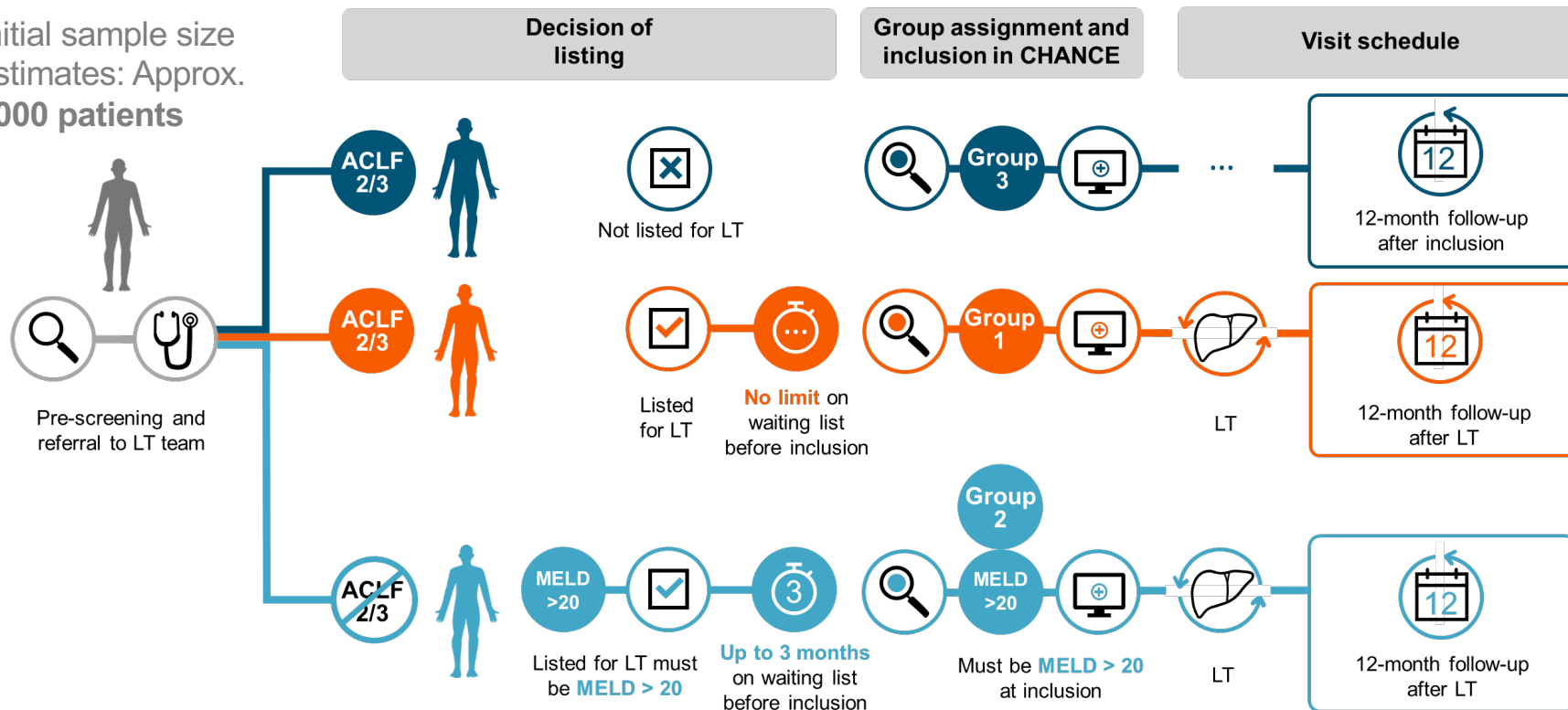
CT scan

Exploratory objectives

- To assess the predictive ability of new biomarkers to predict the prognosis on the waiting list and after LT for patients
- To investigate the impact of LT on systemic disturbances (inflammation, leukocyte dysfunction, metabolic alterations) observed in ACLF
- To explore the mechanisms of liver and extrahepatic organ recovery after LT and determinants of this recovery

CHANCE Study Design in a Nutshell

Initial sample size estimates: Approx. 2000 patients



CHANCE Participating Centers

67
OPEN
CENTERS

63
RECRUITING
CENTERS
21 COUNTRIES

**NORTH
AMERICA**
15 CENTERS

**LATIN
AMERICA**
8 CENTERS

EUROPE
53 CENTERS

ASIA
15 CENTERS

OCEANIA
2 CENTERS

92
CENTERS
10 TIME ZONES



CHANCE Progress Report for the Month of October 2023



Group 1
ACLF 2/3



Listed for
liver
transplantatio
n



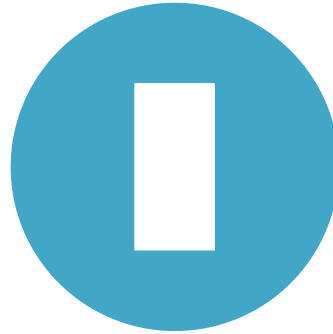
Group 2 > 1
developing
ACLF 2/3



MELD
>20

Group 2
no ACLF 2/3

MELD >20 when
added to waiting
list
and at inclusion
Listed for liver
transplantation



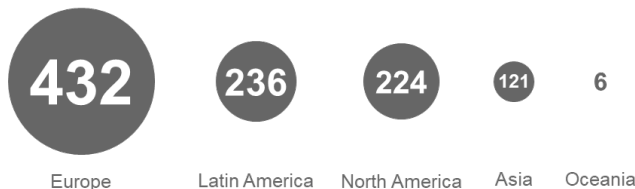
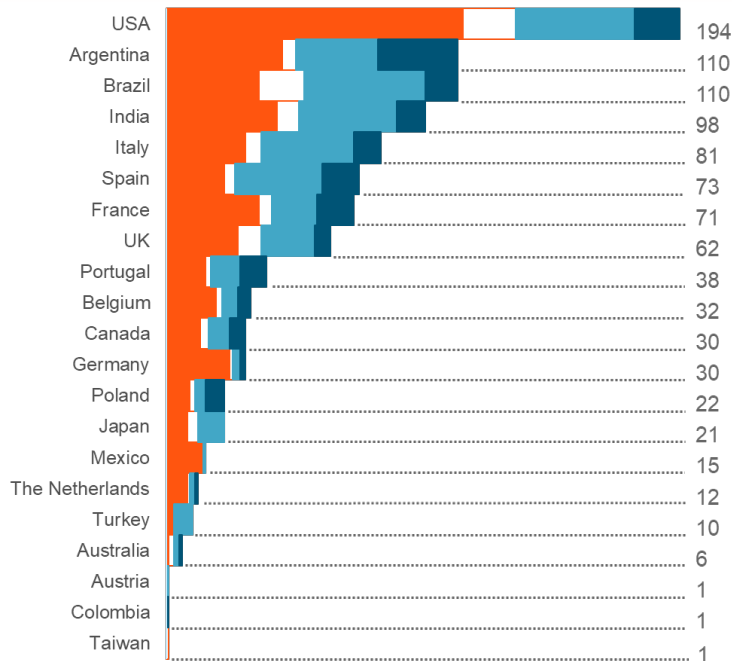
Group 3
ACLF 2/3



Not listed for
liver transplantation

1019
patients

Patients Recruited by Continent and Country



Group 1



Group 2



Developing ACLF 2/3 Listed | MELD > 20

Group 3



Interim Assessment

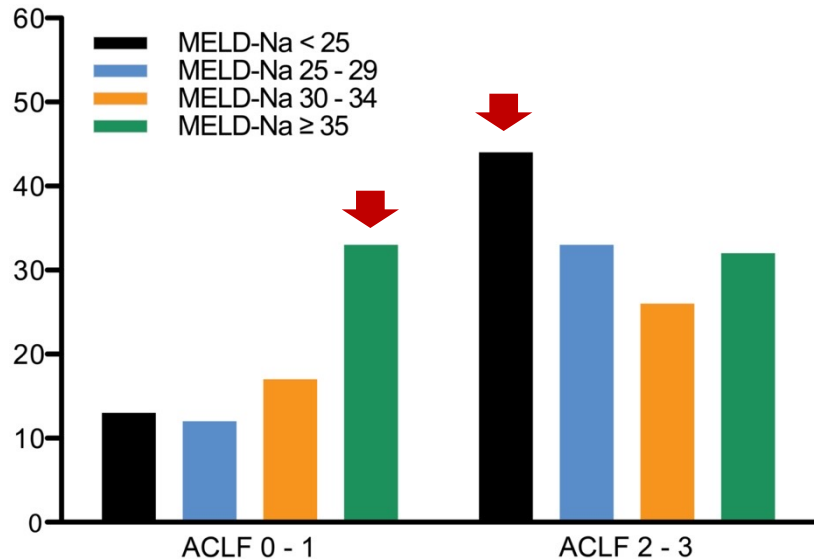
Primary Objective

N = 594	G1 (ACLF 2–3)	G2 (ACLF 0–1)	G2 (ACLF 0–1) developing ACLF 2–3	G3 (ACLF 2–3)
Overall mortality before LT	30%	13%	30%	90%
Transplants	69%	82%	63%	-
3-month mortality after LT	10%	5%	10%	-

Interim Assessment

Primary Objective

Risk of death or delisting	MELD-Na < 25	25 < MELD-Na < 29	30 < MELD-Na < 34	MELD-Na ≥ 35
ACLF 0–1 (<i>n</i> = 195)	13% (<i>n</i> = 38)	12% (<i>n</i> = 94)	17% (<i>n</i> = 60)	33% (<i>n</i> = 3)
ACLF 2–3 (<i>n</i> = 251)	44% (<i>n</i> = 9)	33% (<i>n</i> = 27)	26% (<i>n</i> = 78)	32% (<i>n</i> = 137)



Risk of death or delisting according to ACLF grade and MELD-Na score stratification. Of note, sample size in the extremes is too small to provide confident estimates (i.e., ACLF 2–3 with low MELD-Na, ACLF 0–1 with large MELD-Na).

Interim Assessment

Primary Objective

Outcomes of transplanted patients with confident follow-up of 3M according to their LT date

N = 378	3-Month mortality after LT	
	First 200 patients	Second 178 patients
Overall	7%	8%
G1 (ACLF 2–3)	9%	11%
G2 (ACLF 0–1)	5%	6%

ACLF and Liver Transplantation

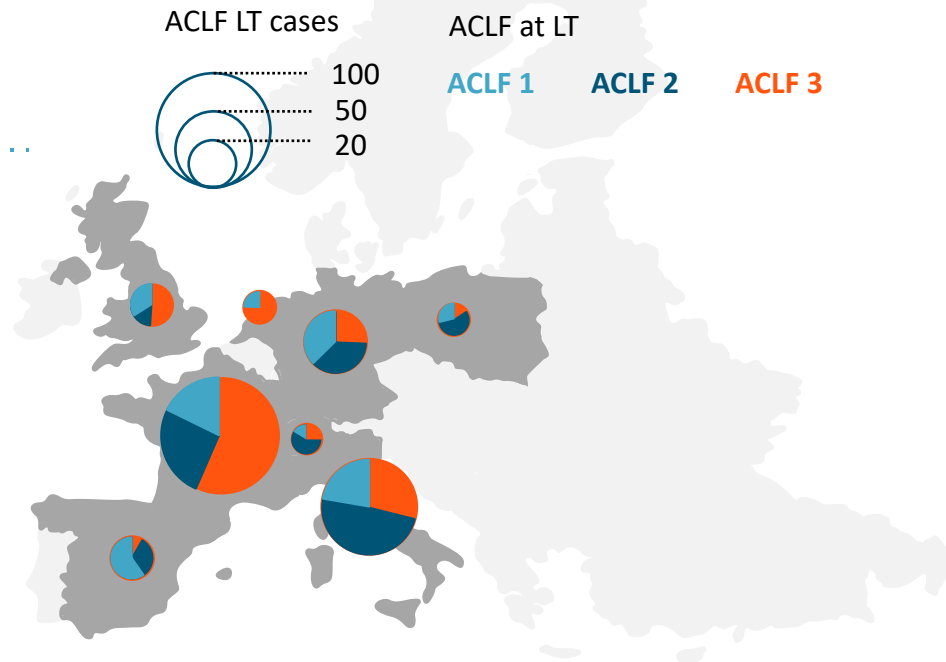
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The European Perspective: Lack of Equity of Access

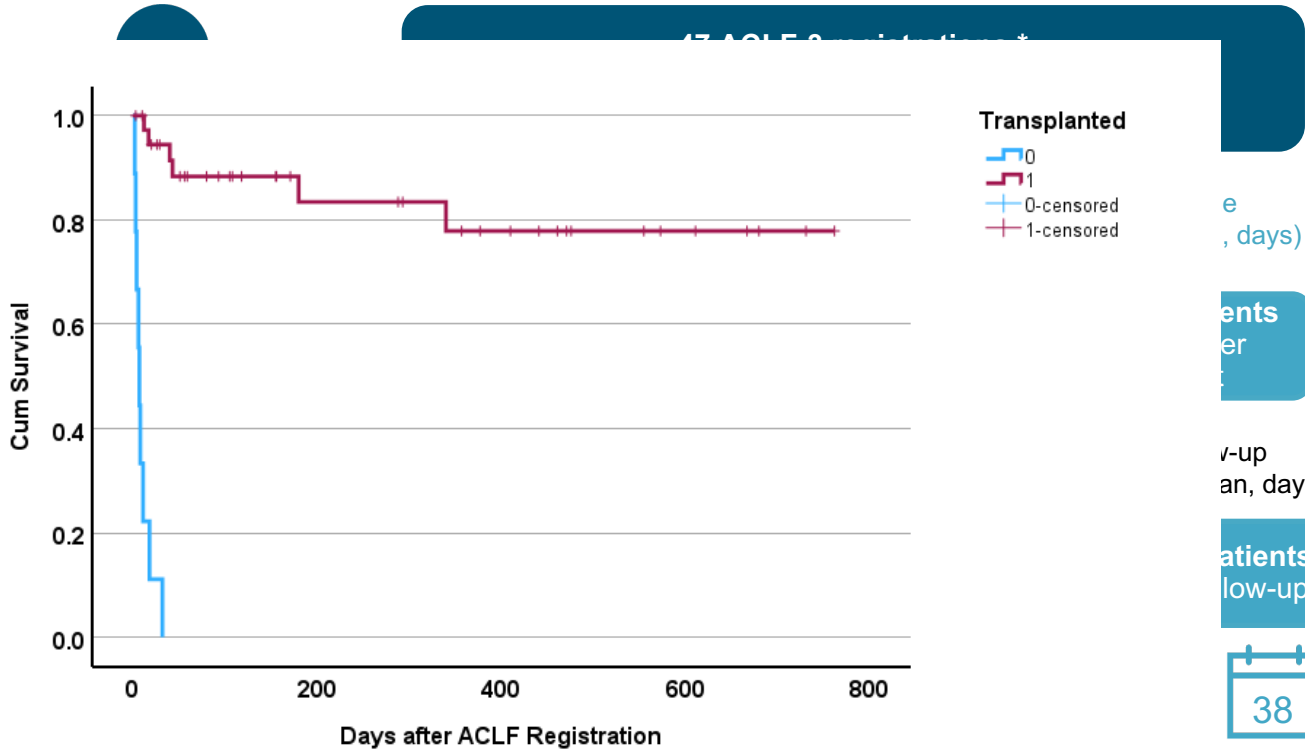
A collaborative study between EF Clif, ELITA and ELTR

Country	No. of centers	No. of LTs	DCC indication (95% CI)	ACLF 2-3 at LT (95% CI)
Italy	7	891	40.3% (37.1–43.6)	13.6% (10.3–17.6)
France	4	613	51.5% (47.5–55.6)	26.9% (22.1–32.1)
United Kingdom	2	495	55.6% (51.1–60.0)	2.9% (1.3–5.7)
Spain	2	229	44.1% (37.6–50.8)	5.0% (1.6–11.2)
Poland	1	184	24.5% (18.4–31.3)	8.9% (2.5–21.2)
The Netherlands	1	114	51.8% (42.2–61.2)	6.8% (1.9–16.5)
Germany	2	85	48.2% (37.3–59.3)	41.5% (26.3–57.9)
Switzerland	1	66	39.4% (27.6–52.2)	15.4% (4.4–34.9)



UK Service Development Evaluation to Transplant ACLF-3 With Priority Using ACLF-Specific Criteria (May 2021–April 2023)

43 yr M
2.2 (1.5–2.8) L
3.5 (1–4) F



Data courtesy of Professor William Bernal; AASLD 2023 (abstract).

ICU stay
hospital stay
(median, days)

Conclusions

- Liver Transplantation saves the lives of patients with severe ACLF
- The current allocation systems based on the MELD score underestimate the risk of death of patients with severe ACLF
- Data suggests wide variations in practice with lack of equity of access of ACLF patients to LT
- Advanced age, Respiratory failure, Uncontrolled or fungal infection, increasing inotrope requirements and severe lactatemia are associated with increased risk of death
- UK Pilot program should be replicated across the world
- The global CHANCE study will address important questions
- Early data shows great engagement and encouraging data.....



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Giovanni Tritto
Montse De Oca
Fausto Andreola
Luisa Baker
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Dev Katarey
Su Lin
Qianwen Zhou

Sheida Rezaa
Andrea Krstevski
Ahmed El-Shabrawi
Wenting Tan
Mapi Ballester
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Fuyang Xian
Kohi Gananandan
Mahdi Saeidinejad
Supachaya Sriphoosanaphan
Jinxia Liu



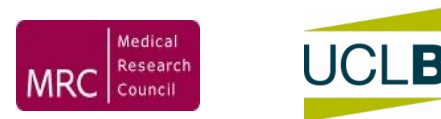
wellcome trust

NIHR | National Institute
for Health Research



NHS
Royal Free London
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CARBALIVE



YAQRIT



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Framework Programme of the
European Union