

# MÁSTER EN HEPATOLOGÍA

**UAM**  
Universidad Autónoma  
de Madrid

 Universidad  
de Alcalá

Asignatura: Trasplante Hepático

## “Trasplante hepático en pacientes con ACLF”

Rosa Martín Mateos

Hospital Universitario Ramón y Cajal, IRYCIS, Universidad de Alcalá, CIBERehd,  
Madrid

# ¿Por qué hablar del trasplante en el ACLF?



¿Tienen distinto pronóstico los pacientes trasplantados con ACLF?

¿Por qué tienen distinto pronóstico?  
Particularidades a tener en cuenta:  
Dinámico, fallo de órgano e  
inflamación sistémica de alto grado

¿Futilidad?

¿Sirven las mismas escalas de  
futilidad que para otros pacientes?

¿Cómo se valora el  
pronóstico?

¿Hay que priorizarlos?  
¿qué pasa con el resto de los pacientes en lista?

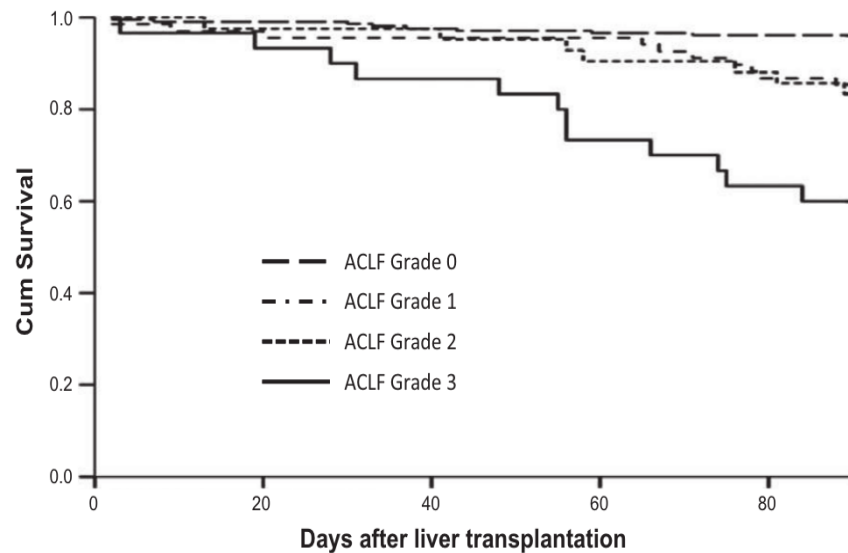


# 1. El ACLF impacta negativamente en el pronóstico tras el trasplante



DIGESTIVO  
RAMON Y CAJAL  
MADRID

## Impact of acute-on-chronic liver failure on 90-day mortality following a first liver transplantation

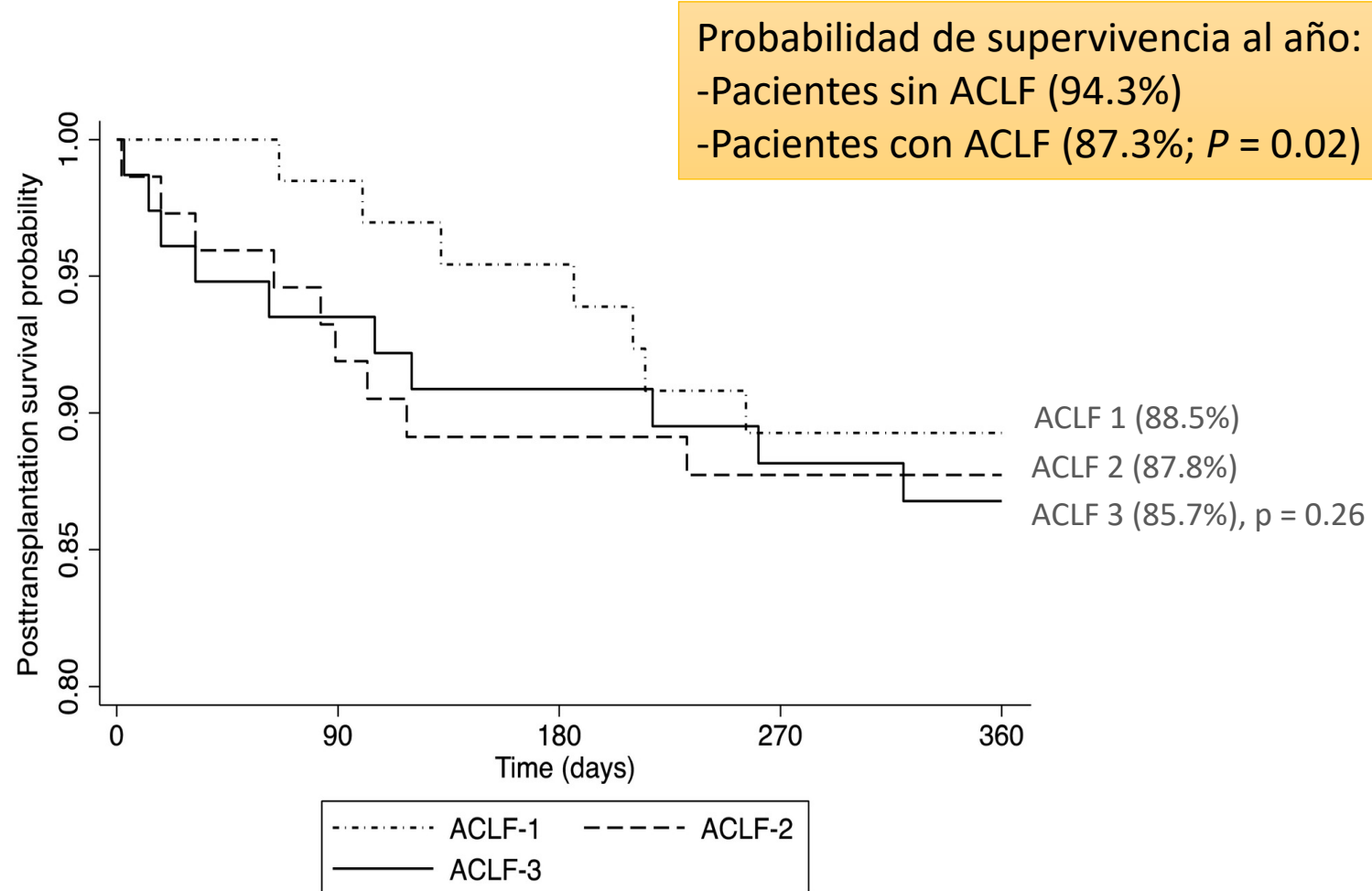


Variable	Beta coefficient	HR	CI 95%	P
Recipient Age ( $\leq 57.2$ vs $> 57.2$ years)	0.40	1.49	1.10-2.03	.010
Infection (no vs yes)	0.44	1.56	1.13-2.14	.006
ACLF (no vs yes)	1.75	5.78	3.42-9.77	<.001
Recipient gender (F vs M)	-0.28	0.76	0.54-1.06	.104
Donor gender (F vs M)	0.29	1.34	0.98-1.83	.065
Aetiology LT (1 vs 2)	-0.29	0.75	0.53-1.04	.088

ACLF, acute-on-chronic liver failure, Aetiology 1: cancer on cirrhosis, 2: end-stage liver disease.

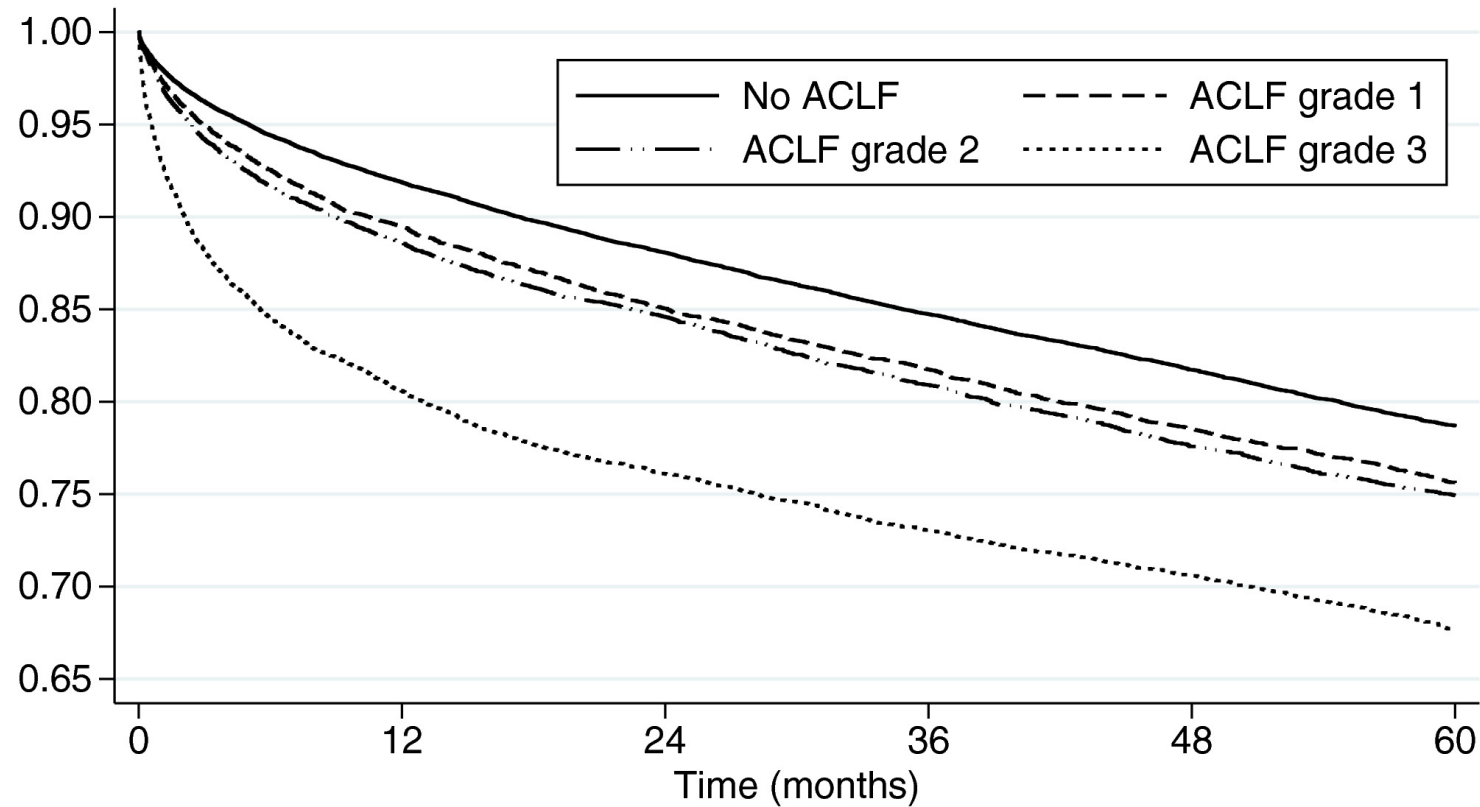
	Total cohort (n=350)	Without ACLF (n=210)	With ACLF (n=140)	P
90-day mortality n (%)	37 (10.6)	8 (3.8)	29 (20.7)	<.001
1-year mortality n (%)	60 (17.1)	18 (8.6)	42 (30)	<.001

# 1. El ACLF impacta negativamente en el pronóstico tras el trasplante

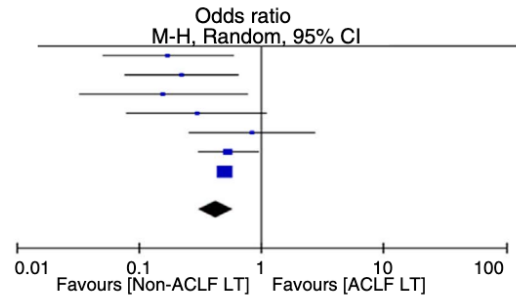


# 1. El ACLF impacta negativamente en el pronóstico tras el trasplante

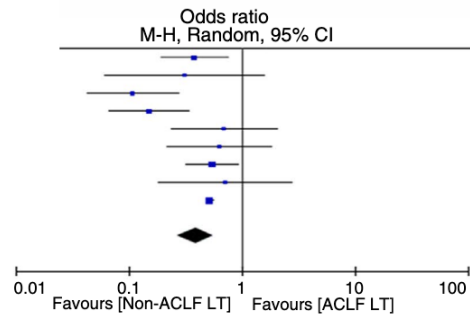
## Posttransplant patient survival probability



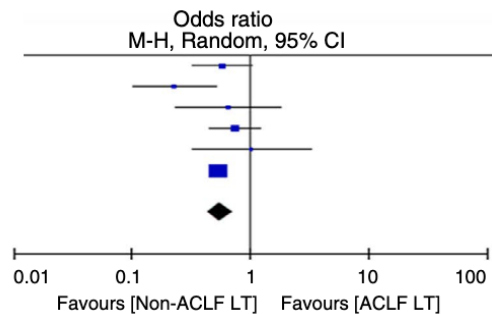
# 1. El ACLF impacta negativamente en el pronóstico tras el trasplante



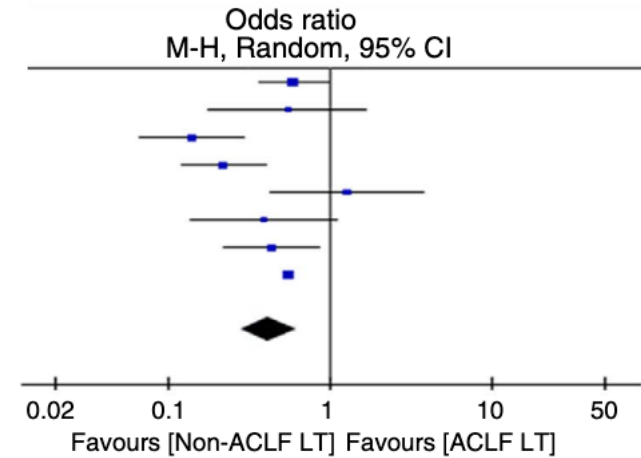
Supervivencia a los 30 días



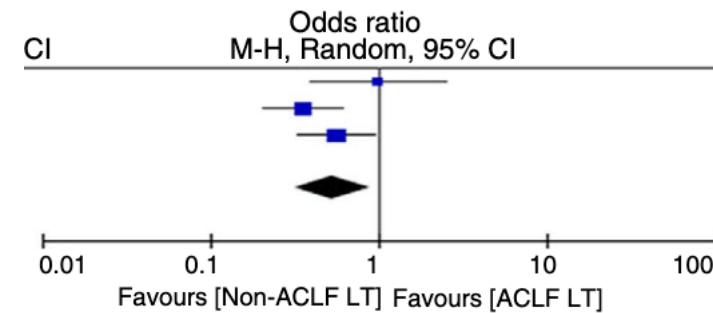
Supervivencia a los 90 días



Supervivencia a los 180 días



Supervivencia al año

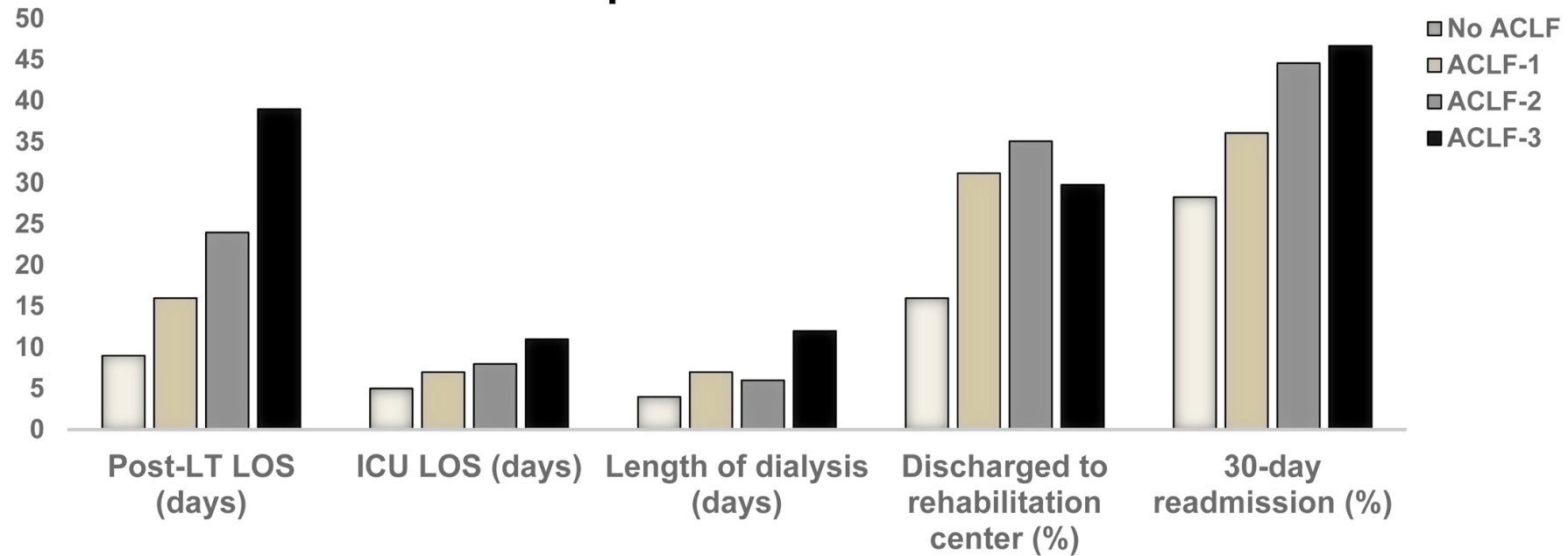


Supervivencia a los 5 años

# Mayor consumo de recursos sanitarios en pacientes trasplantados con ACLF



## Post-transplant healthcare resource utilization



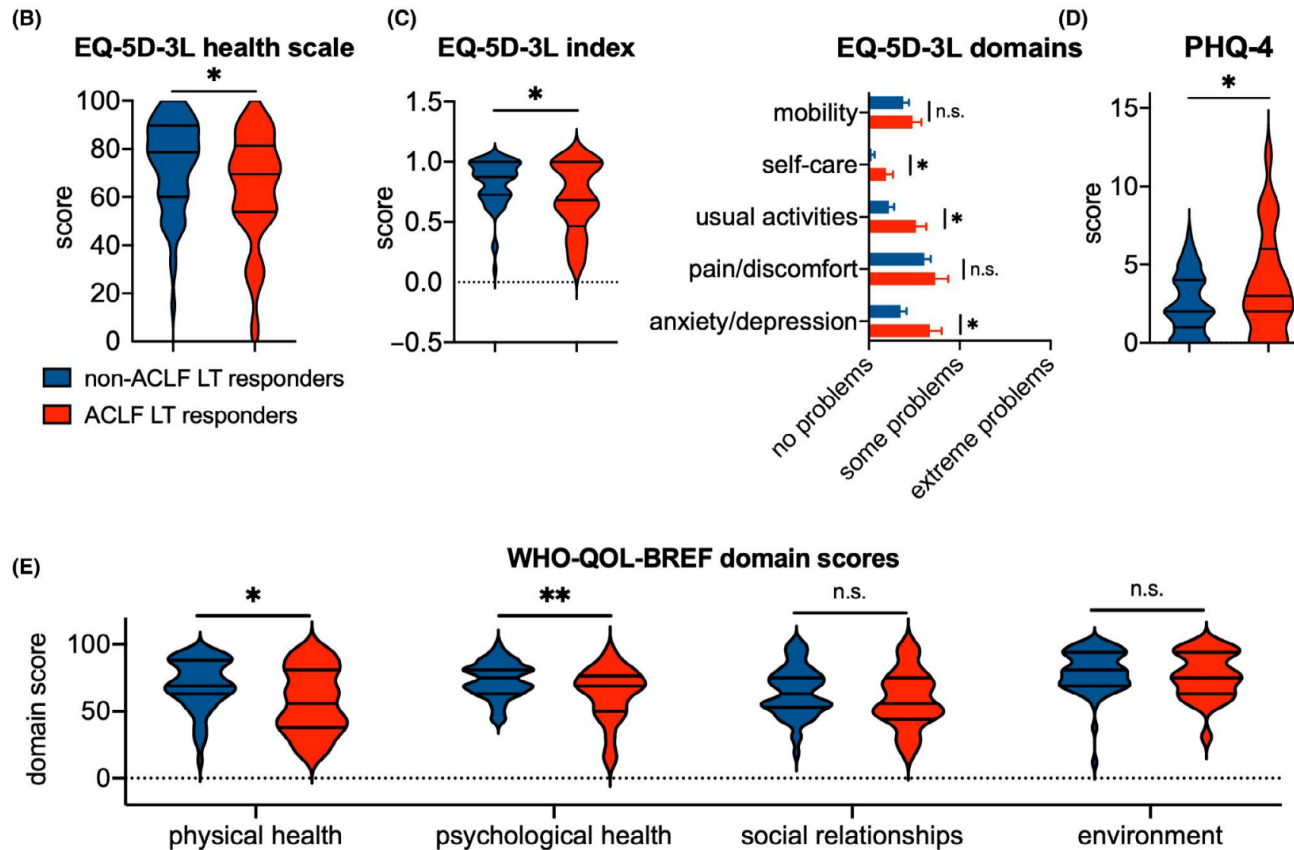


## Liver transplantation for acute-on-chronic liver failure predicts post-transplant mortality and impaired long-term quality of life

Comorbidities 5 years after LT	Non-ACLF LT survivors (n = 120)	ACLF LT survivors (n = 61)	P value
Diabetes mellitus			
Total	60 (50.0%)	22 (38.6%)	.20
New-onset after LT	18 (15.0%)	15 (24.6%)	.15
Hypertension			
Total	99 (79.2%)	48 (84.2%)	.54
New-onset after LT	54 (45.0%)	33 (54.1%)	.27
Dyslipidemia	64 (46.0%)	33 (54.1%)	.36
Osteoporosis	51 (39.2%)	31 (50.8%)	.16
Body mass index	25.20 (22.13-29.13)	26.89 (23.67-29.20)	.10
Median no. of daily medications	9 (7-12)	9 (7-12)	.58
Days hospitalized during 60 months following discharge after LT	44.50 (26.25-73.00)	62.50 (35.25-110.50)	<.001



# Calidad de vida tras el trasplante en pacientes con ACLF



While long-term graft function and extrahepatic comorbidities are comparable in ACLF and non-ACLF LT survivors, the strikingly low QoL in many ACLF-LT recipients warrants consideration during follow-up patient care



Beneficio  
del conjunto

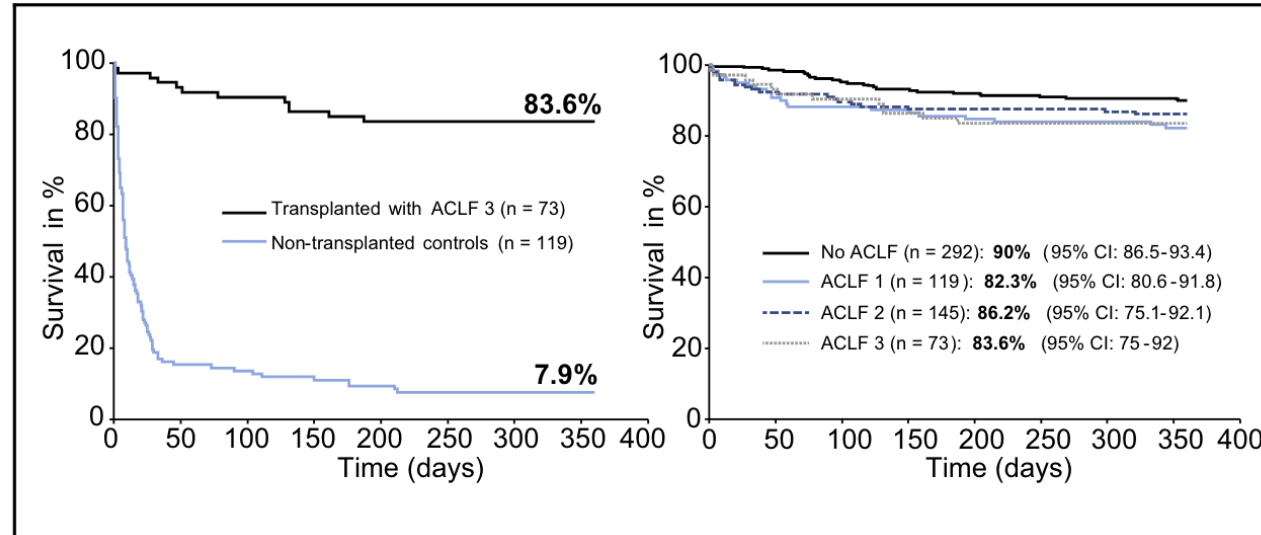
Beneficio  
individual

# El trasplante hepático mejora la supervivencia en pacientes con ACLF-3

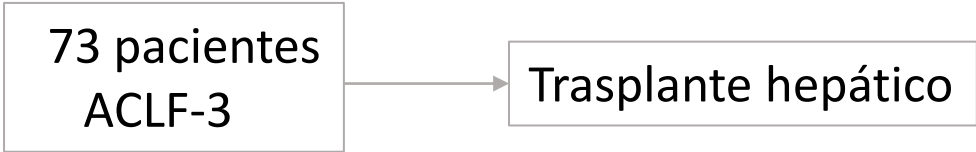


DIGESTIVO  
RAMON Y CAJAL  
MADRID

## Liver transplantation in the most severely ill cirrhotic patients: A multicenter study in acute-on-chronic liver failure grade 3



Beneficio individual



# El trasplante hepático mejora la supervivencia en pacientes con ACLF-3



DIGESTIVO  
RAMON Y CAJAL  
MADRID

## Liver transplantation in the most severely ill cirrhotic patients: A multicenter study in acute-on-chronic liver failure grade 3

Ningún paciente trasplantado con:

- Hemorragia gastrointestinal activa no controlada
- Sepsis < 24h
- Inestabilidad hemodinámica con NA > 3mg/h
- Distress respiratorio agudo ( $PaO_2/FiO_2 < 150$ )

Beneficio  
individual

# El trasplante hepático mejora la supervivencia en pacientes con ACLF-3

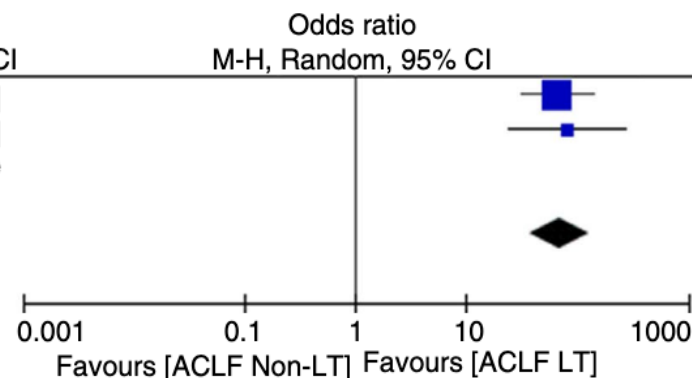


DIGESTIVO  
RAMON Y CAJAL  
MADRID

## Supervivencia al año

Study or subgroup	ACLFLT		ACLF Non-LT		Weight	Odds ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	95% CI
Artru	284	337	9	119	72.7%	65.49	[31.24, 137.28]
Bhatti	55	60	7	59	27.3%	81.71	[24.40, 273.65]
Hong	37	44	69	123		Not estimable	
Total (95% CI)		397		178	100.0%	69.57	[37.01, 130.77]
Total events	339		16				

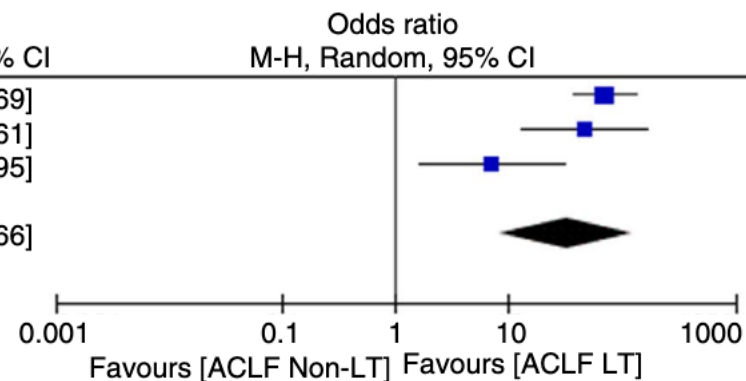
Heterogeneity:  $\tau^2 = 0.00$ ;  $\chi^2 = 0.09$ ,  $df = 1$  ( $P = 0.76$ );  $I^2 = 0\%$   
 Test for overall effect:  $Z = 13.17$  ( $P < 0.00001$ )



## Supervivencia a los 30 días

Study or subgroup	ACLFLT		ACLF Non-LT		Weight	Odds ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	95% CI
Artru	318	337	23	119	40.1%	69.86	[36.50, 133.69]
Bhatti	57	60	17	59	31.2%	46.94	[12.92, 170.61]
Hong	42	44	92	123	28.6%	7.08	[1.62, 30.95]
Total (95% CI)		441		301	100.0%	32.02	[8.50, 120.66]
Total events	417		132				

Heterogeneity:  $\tau^2 = 1.03$ ;  $\chi^2 = 8.45$ ,  $df = 2$  ( $P = 0.01$ );  $I^2 = 76\%$   
 Test for overall effect:  $Z = 5.12$  ( $P < 0.00001$ )



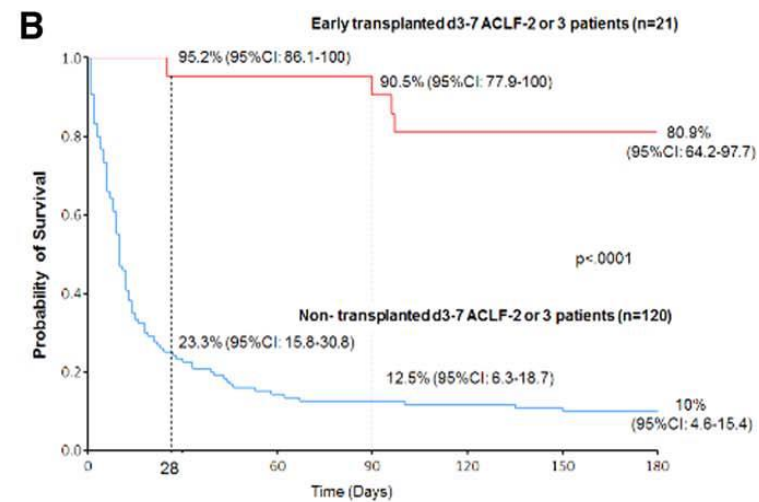
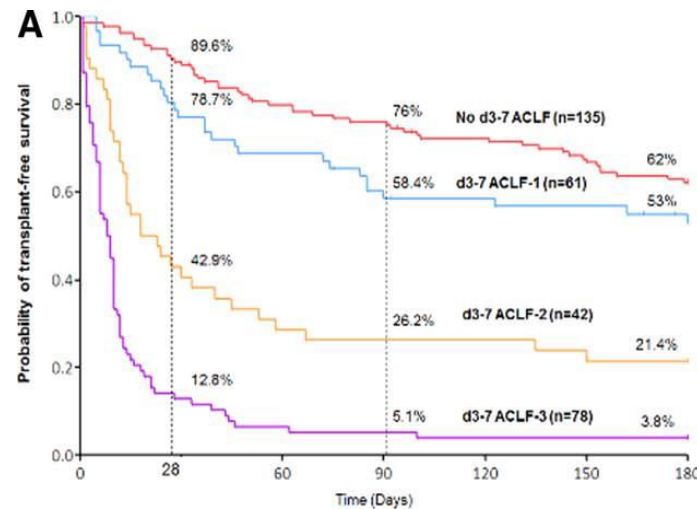
## 2. SD. DINÁMICO – DECISIONES DINÁMICAS



DIGESTIVO  
RAMON Y CAJAL  
MADRID

### Clinical Course of Acute-on-Chronic Liver Failure Syndrome and Effects on Prognosis

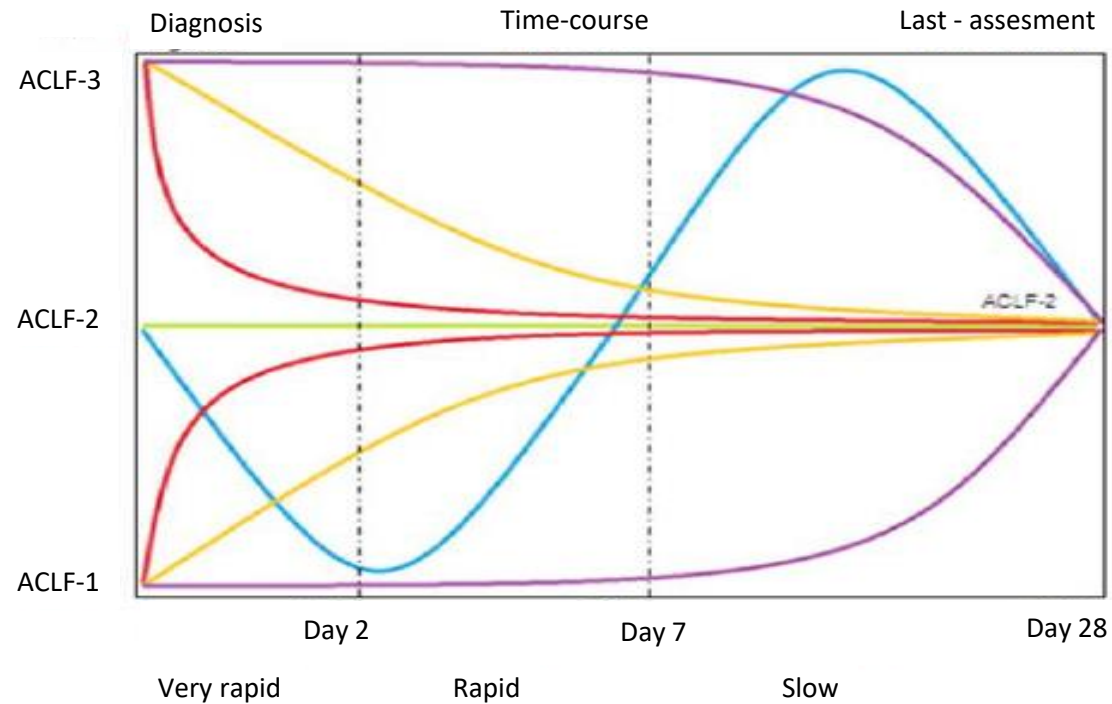
388 pacientes ACLF → Febrero-Sept 2011



4 fallos orgánicos, o CLIF-C ACLFs >64 en los días 3-7, que no se trasplantaron -> Mortalidad 100% a los 28 días

## Clinical Course of Acute-on-Chronic Liver Failure Syndrome and Effects on Prognosis

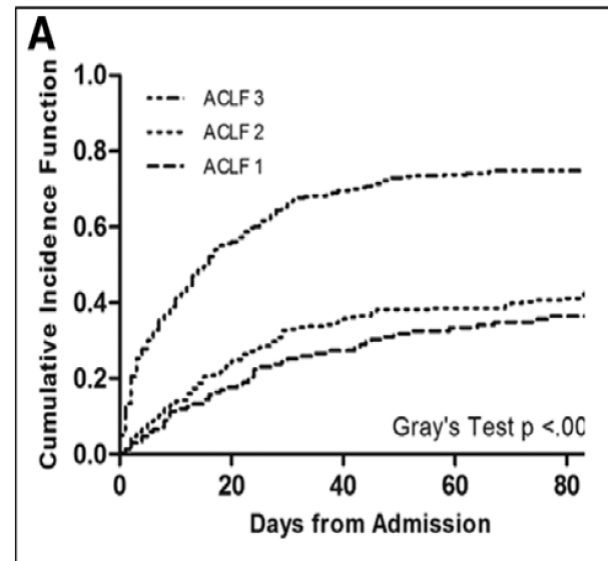
388 pacientes ACLF → Febrero-Sept 2011



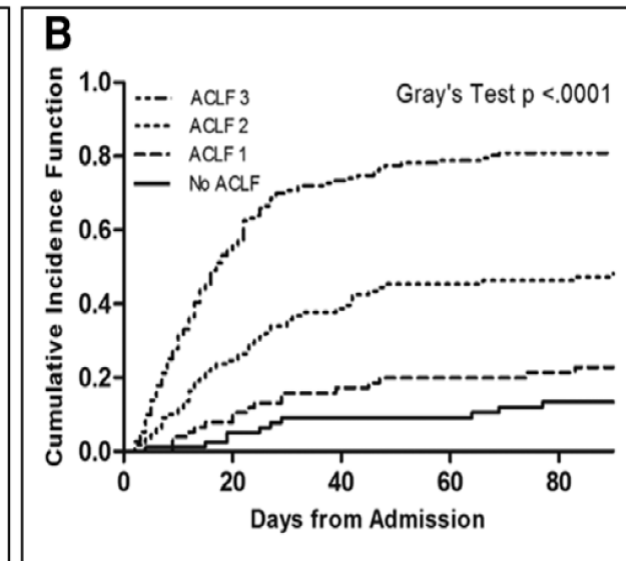
## Dynamic Prognostication in Critically Ill Cirrhotic Patients With Multiorgan Failure in ICUs in Europe and North America: A Multicenter Analysis\*

Incidencia acumulada de muerte o salida de lista

TOTAL: 867 pacientes  
ACLF  
Admitidos en UCI



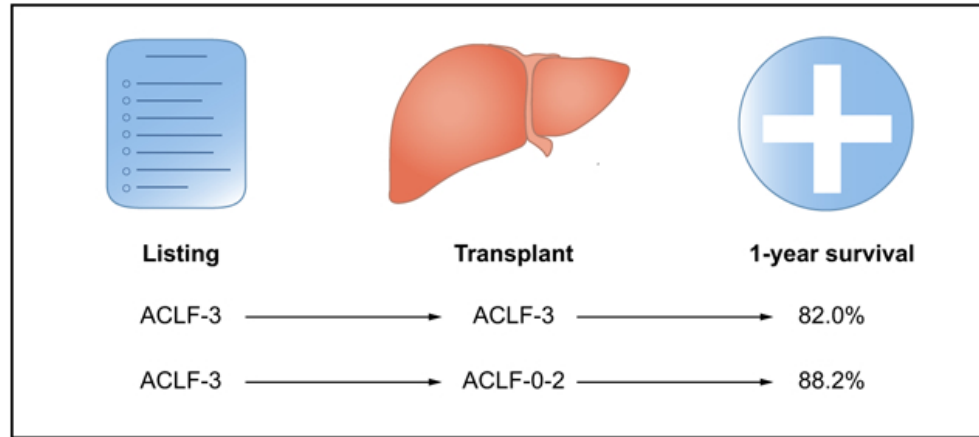
ACLF al ingreso



ACLF a los 3 días

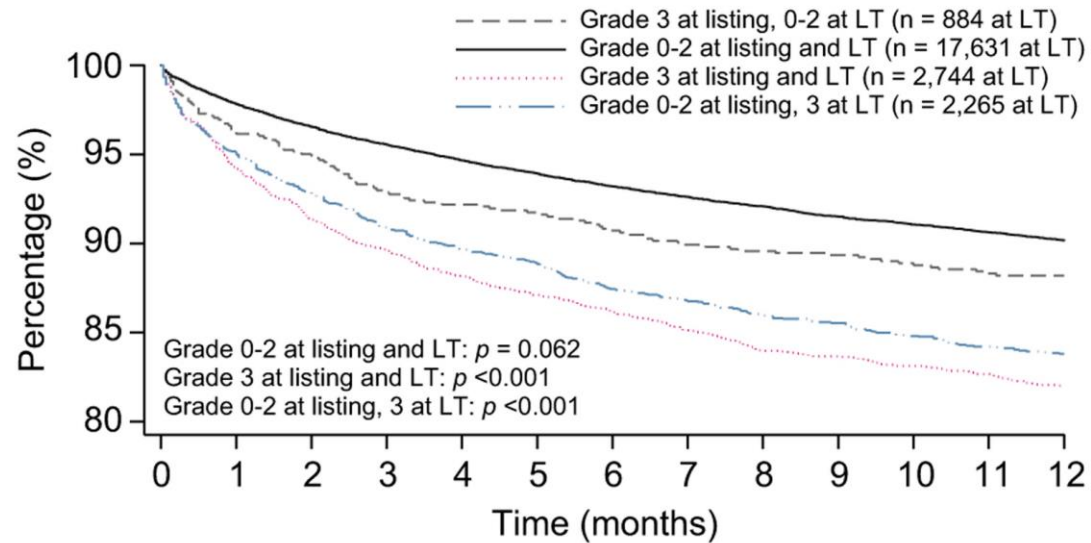


# SD. DINÁMICO – DECISIONES DINÁMICAS

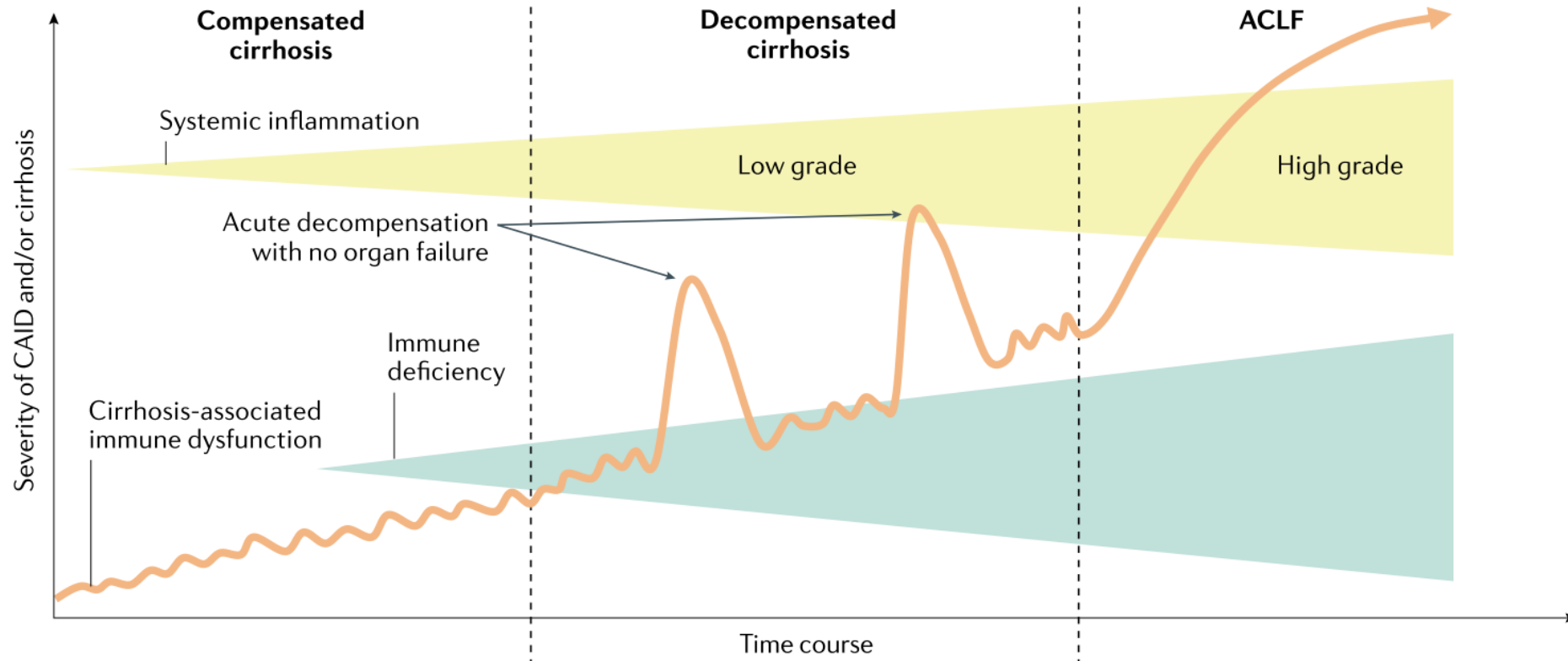


Reevaluar

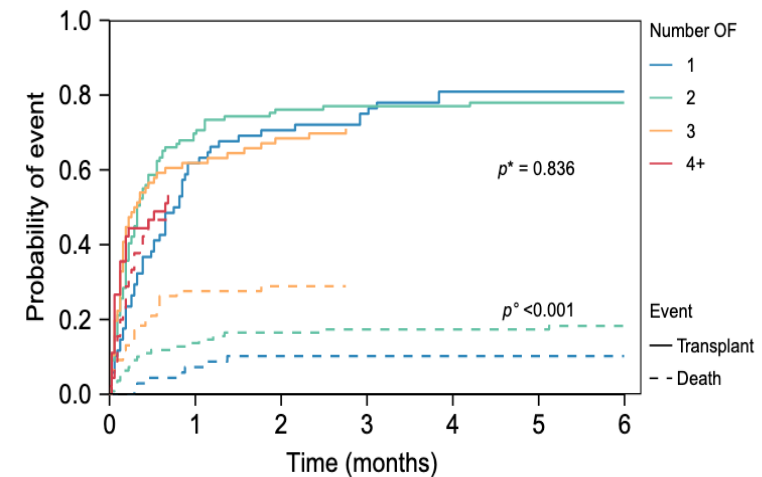
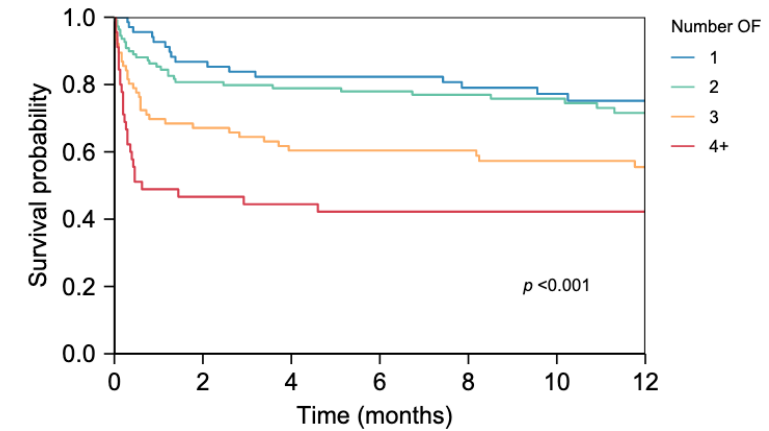
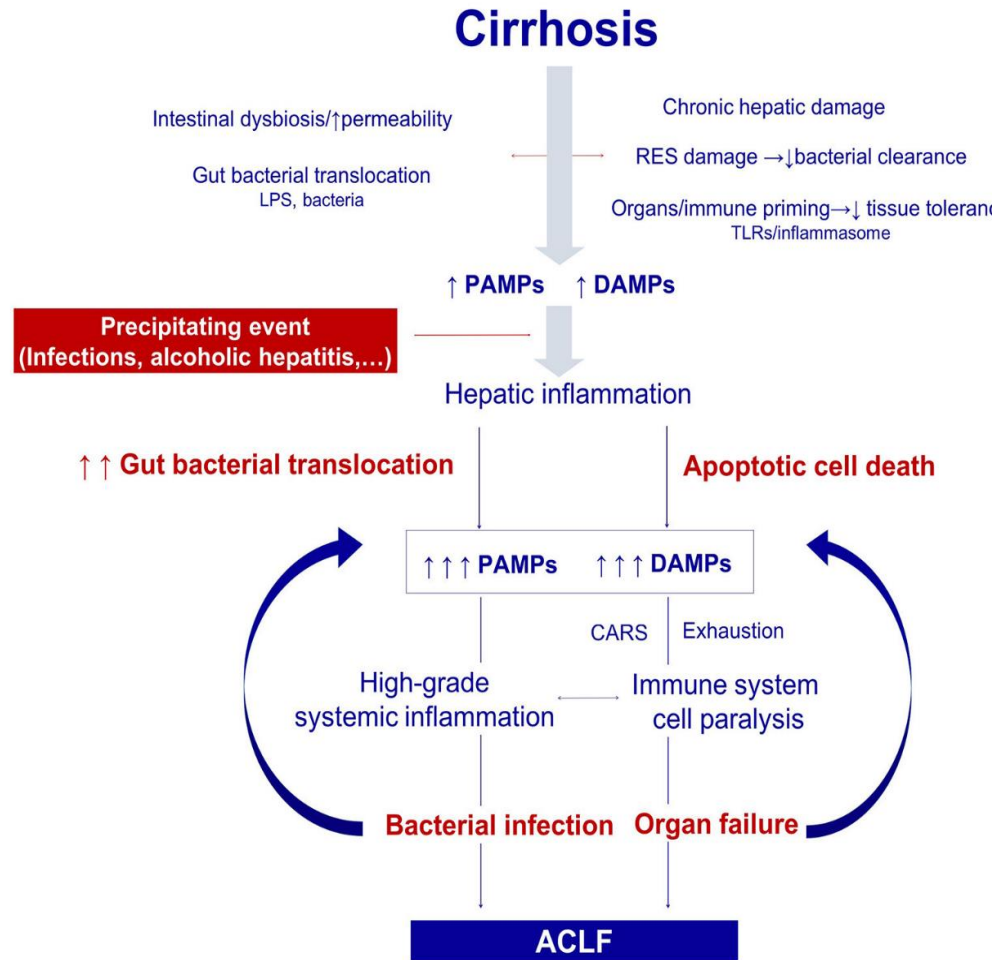
Post-transplant survival probability



# Inflamación sistémica de alto grado e inmunodeficiencia



# Inflamación sistémica de alto grado y fallo de órgano



# Inmunodeficiencia y riesgo de infecciones



	Total cohort (n=350)	Without ACLF (n=210)	With ACLF (n=140)	P
Morbidity before LT n (%)				
Infection	55 (15.7)	4 (1.9)	51 (36.4)	<.001
Cardiac risk	52 (14.9)	26 (12.4)	26 (18.6)	.12
CCI Age-adjusted>6	64 (18.6)	34 (16.2)	30 (21.4)	.25
Ascites	200 (57.1)	93 (44.3)	107 (76.4)	<.001
Hepatic encephalopathy <sup>a</sup>	63 (18)	21 (10)	42 (30)	<.001
Acute variceal bleeding <sup>b</sup>	53 (15)	32 (15)	21 (15)	.95

Variable	Beta coefficient	HR	CI 95%	P
Recipient Age (≤57.2 vs >57.2 years)	0.40	1.49	1.10-2.03	.010
Infection (no vs yes)	0.44	1.56	1.13-2.14	.006
ACLF (no vs yes)	1.75	5.78	3.42-9.77	<.001
Recipient gender (F vs M)	-0.28	0.76	0.54-1.06	.104
Donor gender (F vs M)	0.29	1.34	0.98-1.83	.065
Aetiology LT (1 vs 2)	-0.29	0.75	0.53-1.04	.088

# 3-Predicción de la mortalidad en ACLF



**DIGESTIVO**  
RAMON Y CAJAL  
MADRID

	DATA	CLIF-C Organ Failure Sub-scores
Bilirubin	<input type="text" value="18"/> mg/dl	Liver score <input type="text" value="3"/> Liver failure <input checked="" type="radio"/> Yes <input type="radio"/> No
Creatinine	<input type="text" value="3"/> mg/dl	Kidney score <input type="text" value="2"/> Renal failure <input checked="" type="radio"/> Yes <input type="radio"/> No
Renal replacement therapy	<input type="radio"/> Yes <input checked="" type="radio"/> No	
West-Haven grade for HE	<input type="radio"/> 0 <input type="radio"/> 1 <input checked="" type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4	Brain score <input type="text" value="2"/> Cerebral failure <input type="radio"/> Yes <input checked="" type="radio"/> No
INR	<input type="text" value="3"/>	Coagulation score <input type="text" value="3"/> Coagulation failure <input checked="" type="radio"/> Yes <input type="radio"/> No
MAP	<input type="text" value="60"/> mmHg	Circulatory score <input type="text" value="2"/> Circulatory failure <input type="radio"/> Yes <input checked="" type="radio"/> No
Use of vasopressors (Circulatory failure indication)	<input type="radio"/> Yes <input checked="" type="radio"/> No	
Select one: <input checked="" type="radio"/> PaO <sub>2</sub> (preferred) <input type="radio"/> SpO <sub>2</sub>	<input type="text"/> mmHg <input type="text" value="90"/> %	Lung score <input type="text" value="1"/> Respiratory failure <input type="radio"/> Yes <input checked="" type="radio"/> No
FiO <sub>2</sub>	<input type="text" value="21"/> %	
Mechanical Ventilation	<input type="radio"/> Yes <input checked="" type="radio"/> No	
		Total Number Failures <input type="text" value="3"/> CLIF Organ Failure Score <input type="text" value="13"/>
		<b>i</b> ACLF Grade <input type="text" value="ACLF-Grade 3"/>

# 3-Predicción de la mortalidad en ACLF



**DIGESTIVO**  
RAMON Y CAJAL  
MADRID

## CLIF-C ACLF Score calculation

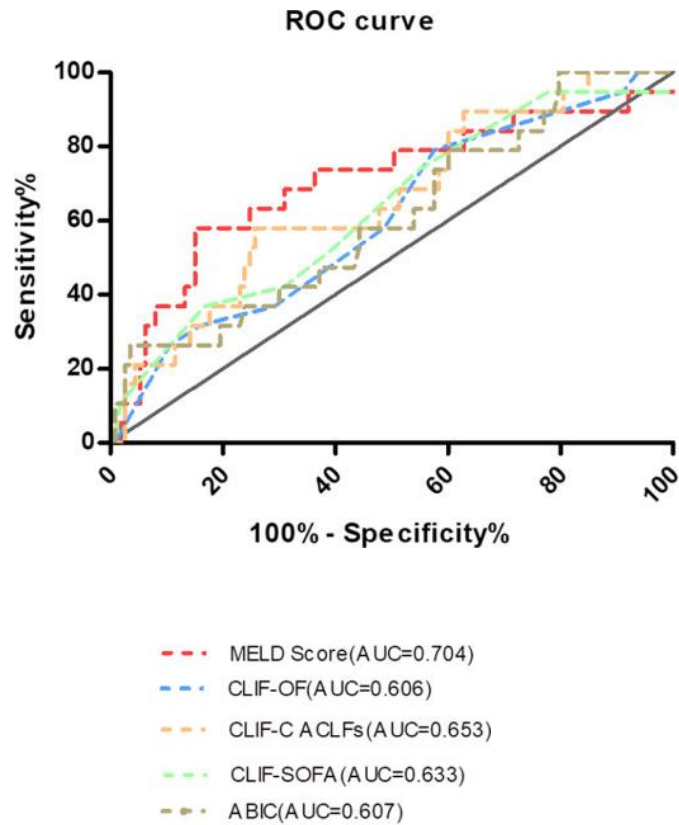
DATA		CLIF-C ACLF Score and probability of dying	
Age	<input type="text" value="56"/> years		
White-cell count	<input type="text" value="50"/> 10 <sup>9</sup> cells/L		
		CLIF-C ACLF Score	<input type="text" value="70"/>
		Probability of dying at 1 month	<input type="text" value="90"/> %
		Probability of dying at 3 month	<input type="text" value="97"/> %
		Probability of dying at 6 month	<input type="text" value="97"/> %
		Probability of dying at 12 month	<input type="text" value="98"/> %

# 3-Predicción de la mortalidad en ACLF

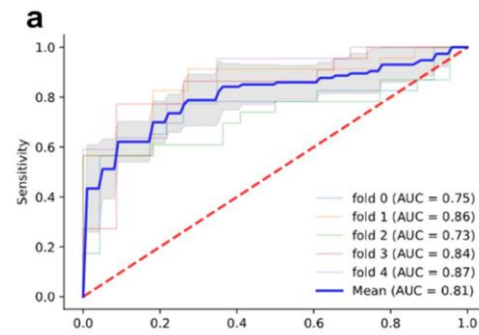


**DIGESTIVO**  
RAMON Y CAJAL  
MADRID

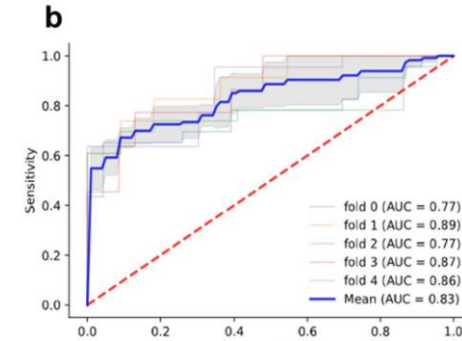
## Modelos clásicos



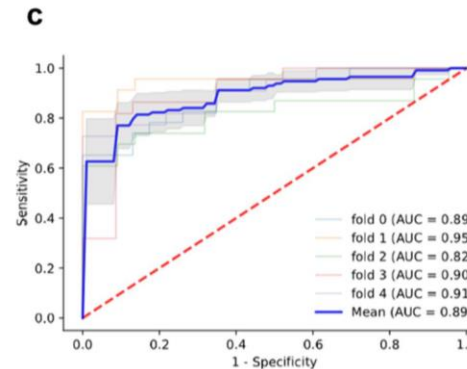
## Inteligencia artificial



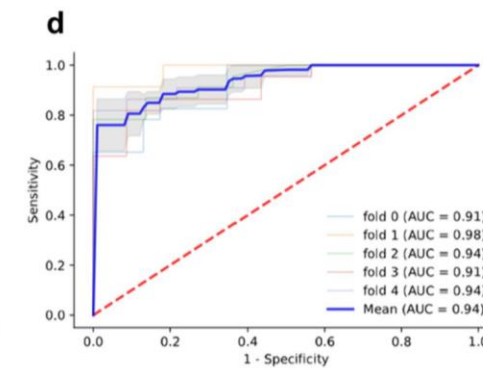
Support vector machine (SVM)



Logistic regression (LR)



Multi-layer perceptron (MLP)



Random Forest

# Pronóstico dinámico



DIGESTIVO  
RAMON Y CAJAL  
MADRID

The ACLF-JM is used to predict survival in liver transplant (LT) candidates with and without ACLF. Because ACLF is dynamic over time, it is hypothesized that the ACLF-JM outperforms the currently-used MELD-Na score.

## Hypothesis:

In 30,533 adult LT candidates without ACLF (67%) or with ACLF-1 (16%), ACLF-2 (10%), or ACLF-3 (7%)

Predict survival

**ACLF-JM**

>

**MELD-Na**

- + Longitudinal data
- + Dynamic update
- + Linear and non-linear
- + Relevant predictors
- + Personalized predictions

- One moment in time
- Forgets previous data
- Linear
- Misses predictors
- Population averages

Compared to the MELD-Na, the ACLF-JM could have prioritized patients with low MELD-Na scores (*i.e.*, not identified by MELD-Na), but 5 times higher waiting list mortality

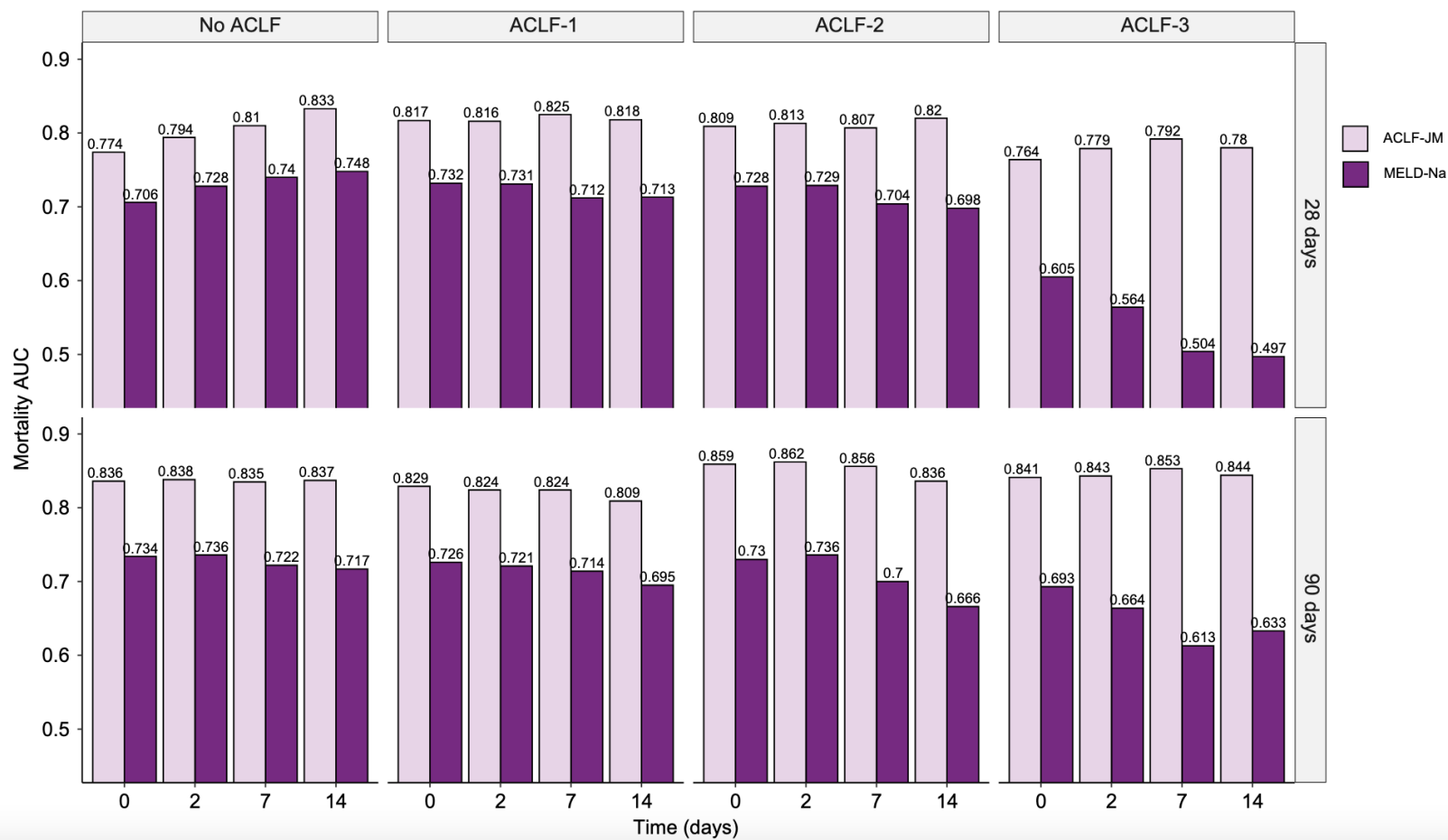
To calculate ACLF-JM mortality predictions given individual patient data, please visit: <https://predictionmodels.shinyapps.io/aclf-jm/>



# Pronóstico dinámico



**DIGESTIVO**  
RAMON Y CAJAL  
MADRID



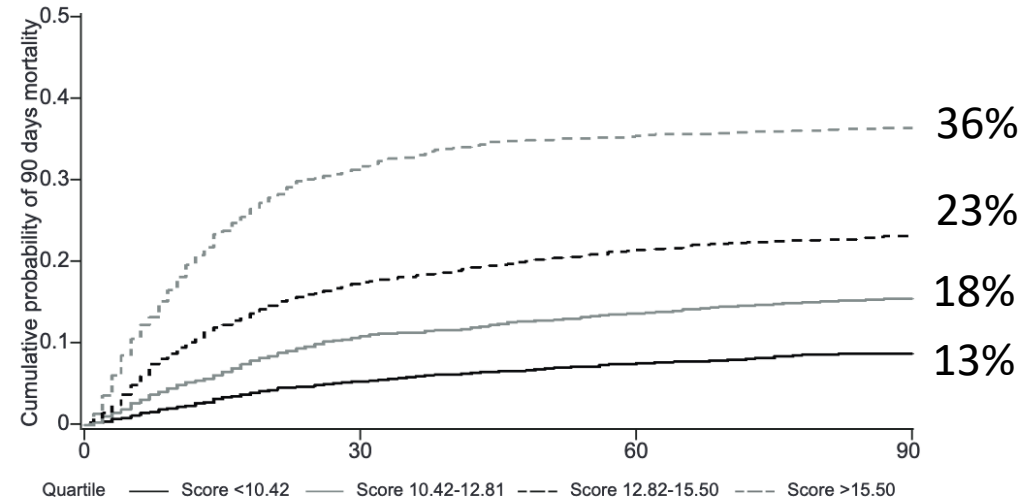
## Validating a novel score based on interaction between ACLF grade and MELD score to predict waitlist mortality

Mohamed A. Abdallah<sup>1</sup>, Yong-Fang Kuo<sup>2</sup>, Sumeet Asrani<sup>3</sup>, Robert J. Wong<sup>4</sup>, Aijaz Ahmed<sup>5</sup>, Paul Kwo<sup>5</sup>, Norah Terrault<sup>6</sup>, Patrick S. Kamath<sup>7</sup>, Rajiv Jalan<sup>8,\*</sup>, Ashwani K. Singal<sup>1,9,\*</sup>

Mortalidad a los 90 días

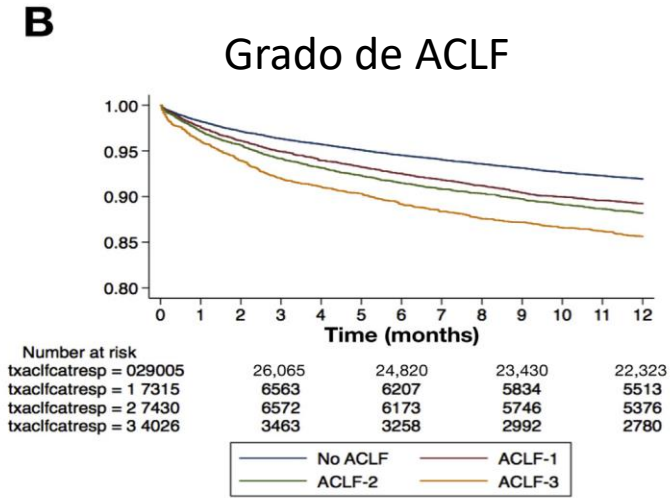
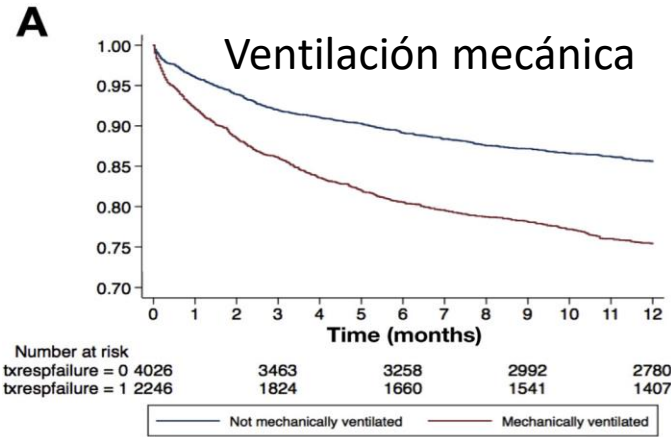
### Variables incluidas:

- Edad
- Sexo
- Etiología
- MELD
- Grado de ACLF
- Obesidad
- Performance status

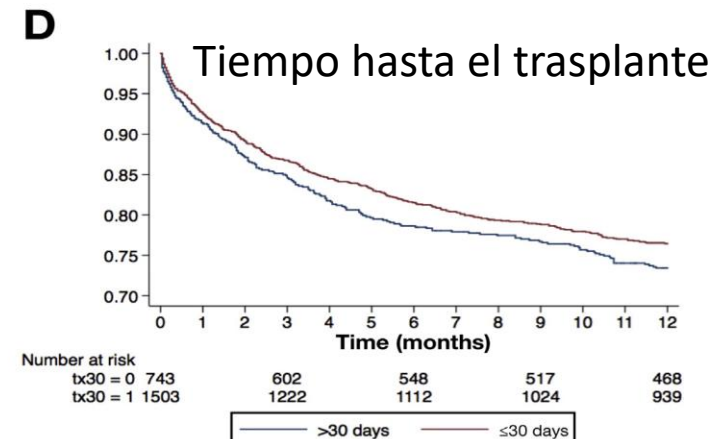
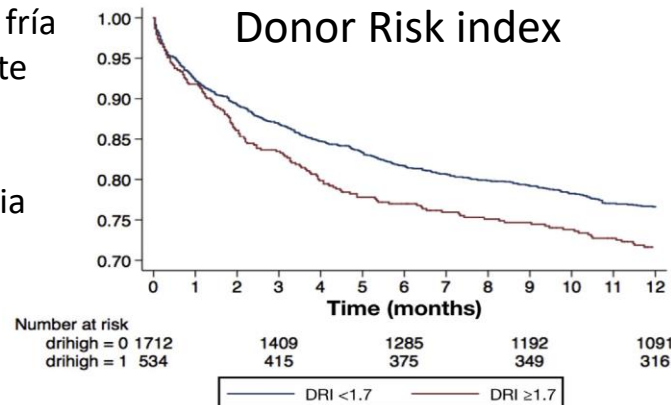


# Factors Associated with Survival of Patients With Severe Acute-On-Chronic Liver Failure Before and After Liver Transplantation

Vinay Sundaram,<sup>1,\*</sup> Rajiv Jalan,<sup>2,\*</sup> Tiffany Wu,<sup>3</sup> Michael L. Volk,<sup>4</sup> Sumeet K. Asrani,<sup>5</sup> Andrew S. Klein,<sup>6</sup> and Robert J. Wong<sup>7</sup>



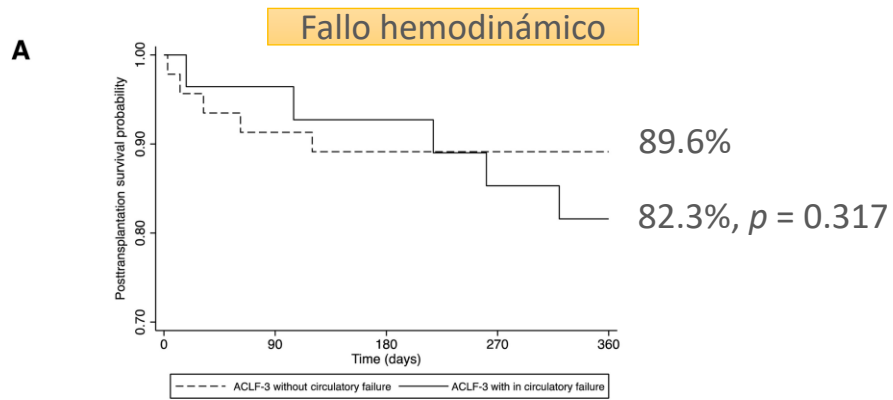
- Edad
- Raza
- Tº isquemia fría
- Causa muerte
- Talla
- Localización
- D. En asistolia
- Parcial



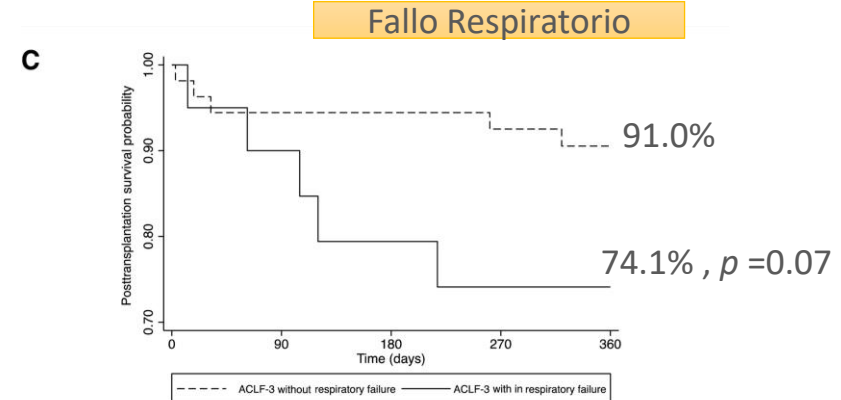
# Predictores de mortalidad tras el trasplante en ACLF 3



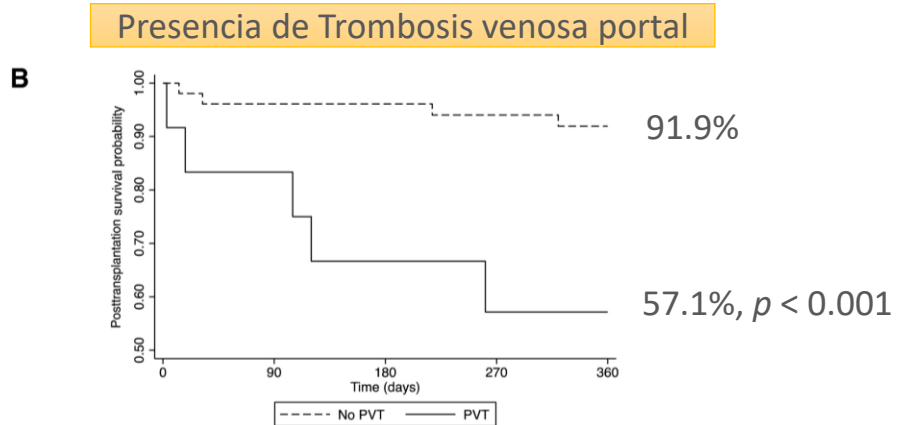
**DIGESTIVO**  
RAMON Y CAJAL  
MADRID



Grade	30 days	90 days	180 days	365 days
No circulatory failure	0.958 (0.844-0.989) n = 47	0.917 (0.793-0.968) n = 45	0.896 (0.768-0.955) n = 43	0.896 (0.768-0.955) n = 40
Circulatory failure	0.966 (0.749-0.895) n = 28	0.966 (0.749-0.895) n = 28	0.929 (0.747-0.982) n = 27	0.823 (0.625-0.922) n = 23



Grade	30 days	90 days	180 days	365 days
No respiratory failure	0.965 (0.867-0.991) n = 56	0.947 (0.846-0.983) n = 55	0.947 (0.846-0.983) n = 54	0.910 (0.798-0.962) n = 48
Respiratory failure	0.950 (0.695-0.993) n = 20	0.900 (0.656-0.974) n = 19	0.794 (0.538-0.917) n = 16	0.741 (0.485-0.883) n = 15



Grade	30 days	90 days	180 days	365 days
No PVT	0.980 (0.869-0.972) n = 51	0.961 (0.852-0.900) n = 50	0.961 (0.852-0.900) n = 48	0.919 (0.799-0.960) n = 43
PVT	0.833 (0.487-0.955) n = 11	0.833 (0.487-0.955) n = 11	0.667 (0.337-0.597) n = 9	0.571 (0.254-0.958) n = 7

## Análisis multivariante:

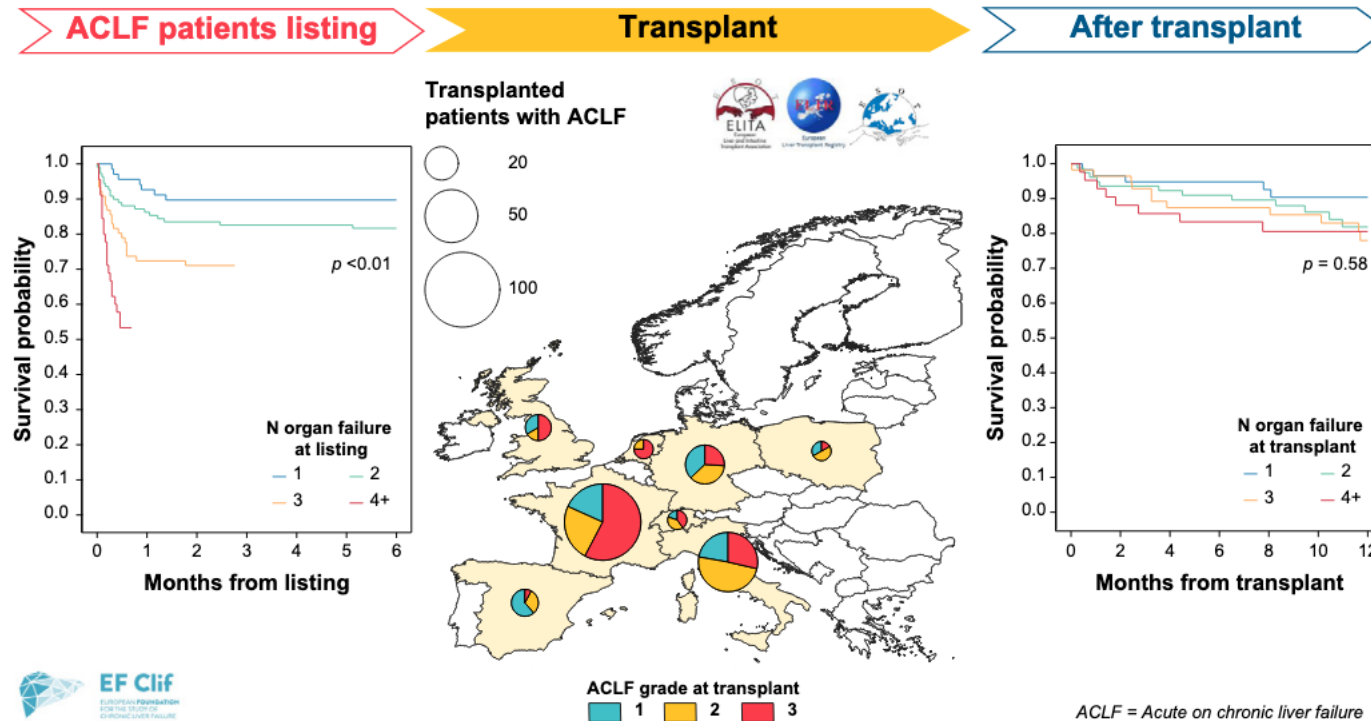
- PVT (OR, 8.33; 95% CI: 2.33-29.7)
- Edad (OR, 1.06; 95% CI: 1.01-1.10)

## 4. ¿Deben priorizarse los pacientes con ACLF?



DIGESTIVO  
RAMON Y CAJAL  
MADRID

### Liver transplantation for patients with acute-on-chronic liver failure (ACLF) in Europe: Results of the ELITA/EF-CLIF collaborative study (ECLIS)<sup>\*</sup>



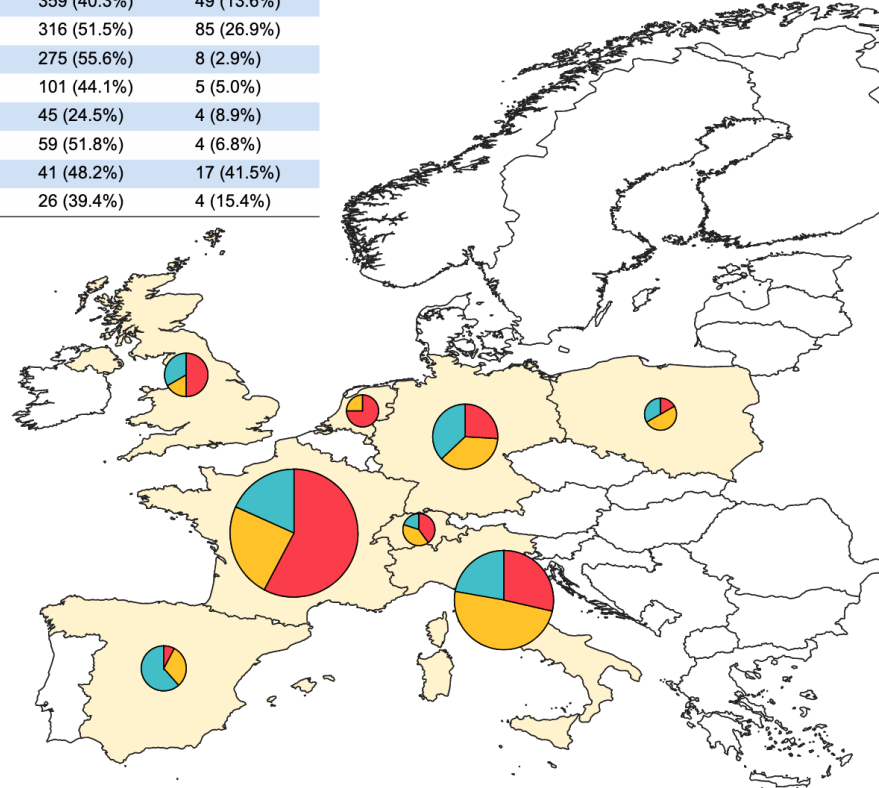
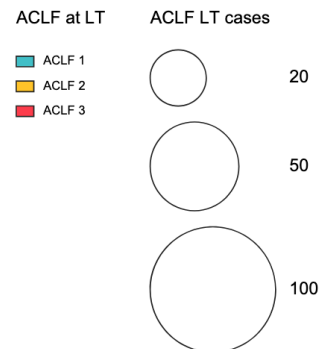
# ¿Deben priorizarse los pacientes con ACLF?



DIGESTIVO  
RAMON Y CAJAL  
MADRID

## Liver transplantation for patients with acute-on-chronic liver failure (ACLF) in Europe: Results of the ELITA/EF-CLIF collaborative study (ECLIS)\*

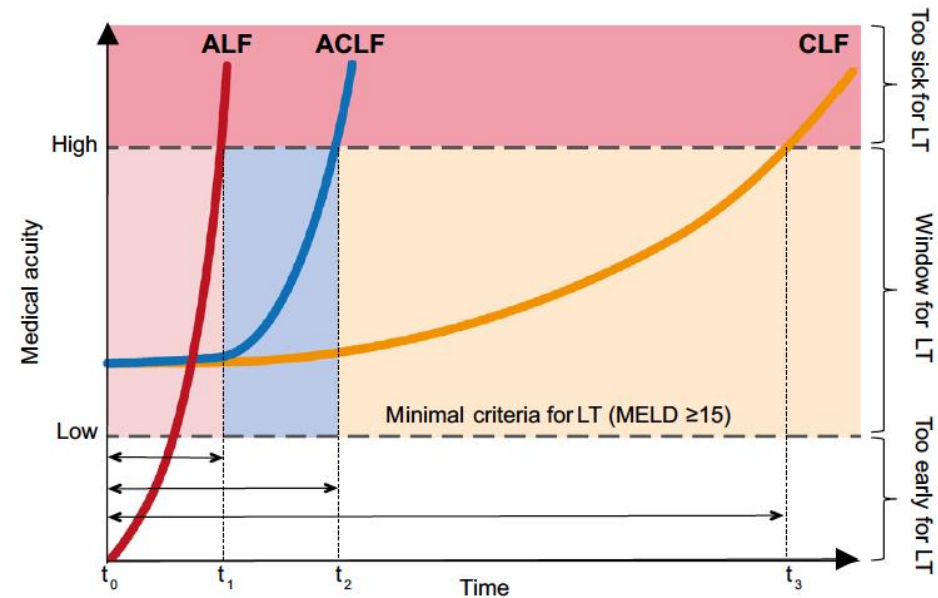
Country	Centres	N of LTs	DC indication	ACLF 2/3 at LT*
Italy	7	891	359 (40.3%)	49 (13.6%)
France	4	613	316 (51.5%)	85 (26.9%)
United Kingdom	2	495	275 (55.6%)	8 (2.9%)
Spain	2	229	101 (44.1%)	5 (5.0%)
Poland	1	184	45 (24.5%)	4 (8.9%)
The Netherlands	1	114	59 (51.8%)	4 (6.8%)
Germany	2	85	41 (48.2%)	17 (41.5%)
Switzerland	1	66	26 (39.4%)	4 (15.4%)



# 5- FUTILIDAD EN ACLF

**Table 2. Specific definitions of post-transplant futile outcome in LT.**

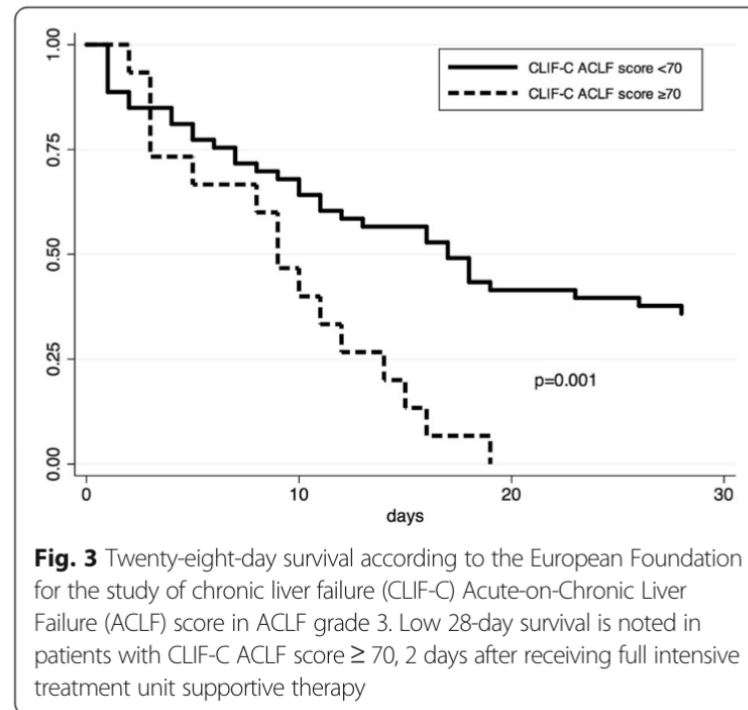
Author, yr	Patient population	Definition of futility
Rana, 2008/2013	Adult recipients	Post-transplant mortality >waiting list mortality
Lao, 2010	Paediatric re-transplant recipients	One-year mortality
Petrowsky, 2014	Adult recipients with MELD $\geq 40$	90-day or in-hospital mortality
Panchal, 2015	Adult recipients with MELD $\geq 40$	90-day mortality
Asrani, 2015	Adult recipients	>50% mortality at five years



El paciente fallece < 3 meses tras el trasplante +/- mortalidad intrahospitalaria



Validation of CLIF-C ACLF score to define a threshold for futility of intensive care support for patients with acute-on-chronic liver failure



CLIF-C ACFL score  $\geq 70$   
a las 48h del ingreso en UVI  
100% mortalidad

Beneficio  
del  
conjunto





## Potentially inappropriate liver transplantation in the era of the “sickest first” policy – A search for the upper limits

Michael Linecker<sup>1,2</sup>, Tanja Krones<sup>3,4</sup>, Thomas Berg<sup>5</sup>, Claus U. Niemann<sup>6,7</sup>, Randolph H. Steadman<sup>8</sup>, Philipp Dutkowski<sup>1,2</sup>, Pierre-Alain Clavien<sup>1,2</sup>, Ronald W. Busuttill<sup>9</sup>, Robert D. Truog<sup>10,11</sup>, Henrik Petrowsky<sup>1,2,\*</sup>

Absolute	Relative
Multiorgan failure with 4 or more organ systems failing (liver, kidney, lungs, circulation, brain)	Increased ventilation support ( $FiO_2 \geq 0.5$ )
Brain oedema plus herniation or absence of cerebral circulation	Intestinal ischaemia
Circulatory failure requiring 2 vasopressors both with limited responsiveness to further dose escalation	Severe frailty secondary to muscle wasting and malnutrition
Pulmonary hypertension with: <ul style="list-style-type: none"> <li>- mPAP &gt;50 mmHg,</li> <li>- mPAP 35–50 mmHg with elevated PVR</li> <li>- &gt;250 dyn/s/cm<sup>5</sup>, or</li> <li>- high PVR &gt;400 dyn/s/cm<sup>5</sup></li> </ul>	Aggregated severe chronic comorbidities
Severe respiratory failure requiring maximal ventilation support ( $FiO_2 \geq 0.8$ , high PEEP) or on ECMO	
Ongoing infections with following features: septic bacteraemia/fungaemia, septic shock, active spontaneous bacterial/fungal peritonitis, tissue invasive fungal infection	
Ongoing severe/necrotising pancreatitis	
Aggregation of several relative conditions	

# ¿Deben priorizarse los pacientes con ACLF?



**DIGESTIVO**  
RAMON Y CAJAL  
MADRID

## CHANCE study

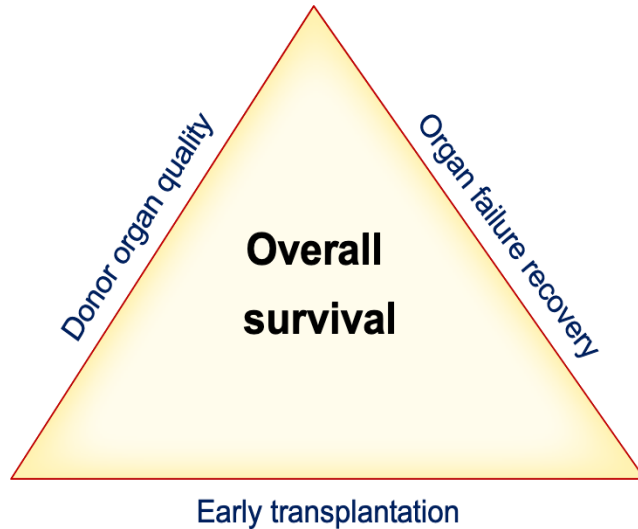
2000 pacientes, 29 países

Prospectivo

Comparar supervivencia de los pacientes con ACLF con trasplante vs no TOH



# ¿Cuándo trasplantar?



## ACLF 3:

- Trasplante precoz maximiza las probabilidades de supervivencia.
- El impacto de utilizar órganos marginales es menor que el de retrasar el trasplante
- La probabilidad de recuperación del fallo orgánico en los 7 primeros días tras la entrada en lista es <10%

# Los pacientes con ACLF-3 tienen mayor riesgo de salir de lista y de mortalidad

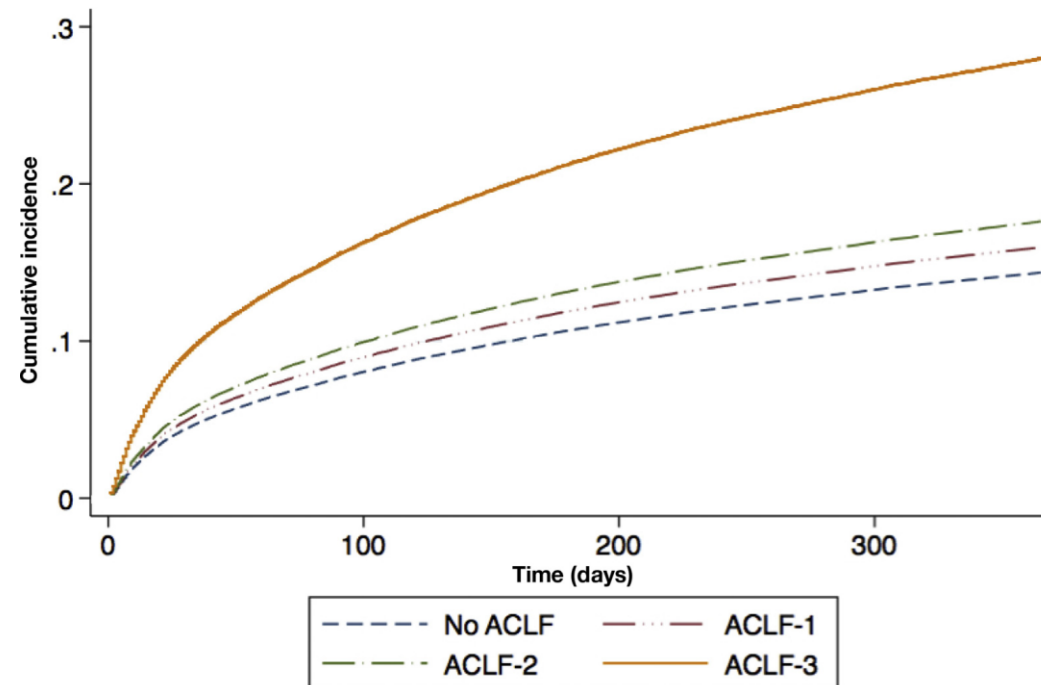


## Incidencia acumulada de muerte o salida de lista

TOTAL: 100594 pacientes  
(2005-2016)

-79% no ACLF

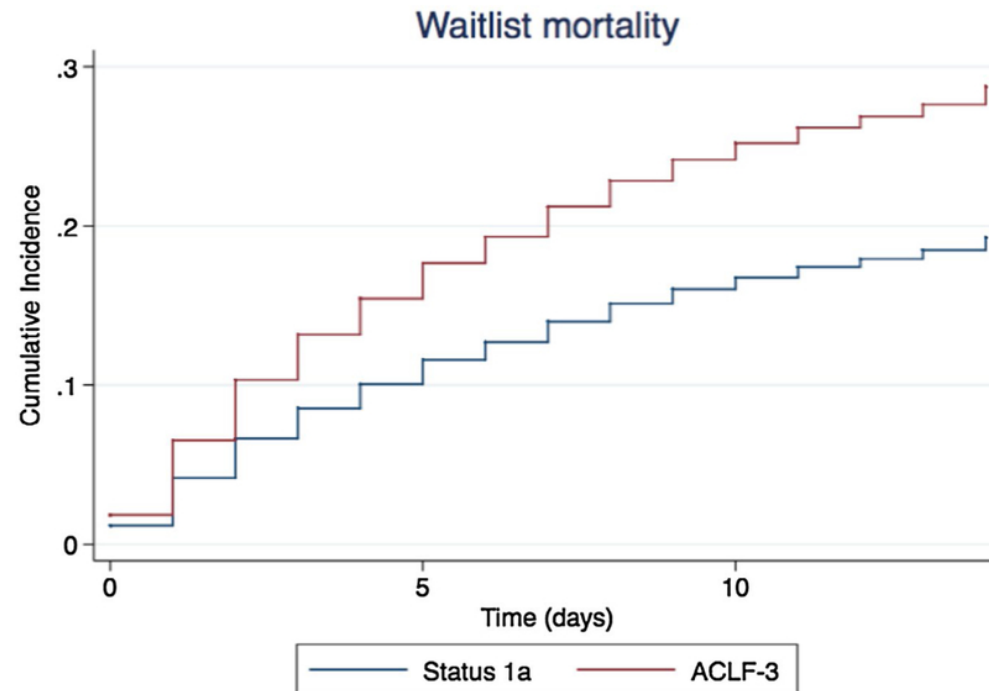
-5,3% (5355) ACLF-3



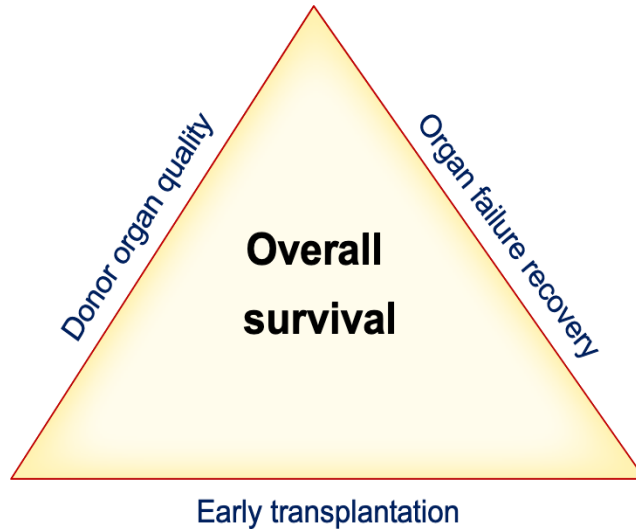
# La mortalidad en lista en pacientes con ACLF-3 es mayor que en los pacientes con ALF



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



# ¿Cuándo trasplantar?



## ACLF 3:

-Trasplante precoz maximiza las probabilidades de supervivencia.

-El impacto de utilizar órganos marginales es menor que el de retrasar el trasplante

-La probabilidad de recuperación del fallo orgánico en los 7 primeros días tras la entrada en lista es <10%

-> Una vez incluido el lista, trasplante precoz aumenta las probabilidades de supervivencia al año

# CONCLUSIONES



DIGESTIVO  
RAMON Y CAJAL  
MADRID

- La **supervivencia** tras el trasplante en pacientes con ACLF es **inferior** a la de los pacientes sin ACLF en el momento de la cirugía
- El ACLF es una situación **dinámica** (reevaluar a los 3-7 días)
- ACLF-3 no es *a priori* contraindicación para el trasplante, aunque tiene un impacto negativo en la supervivencia
- Priorizar de forma individualizada y consensuada
- Futilidad** está estrechamente relacionada con el número y el tipo de fallo de órgano, los requerimientos de soporte vital (cardiovascular y respiratorio) y su evolución (trombosis portal (?))
- Potencial beneficio del **trasplante precoz** vs esperar a la recuperación del fallo orgánico/mayor calidad del órgano trasplantado



 @DigestivoHRyC





# MÁSTER EN HEPATOLOGÍA



UAM  
Universidad Autónoma  
de Madrid



Universidad  
de Alcalá

# 1. Pronóstico tras el TOH en pacientes con ACLF



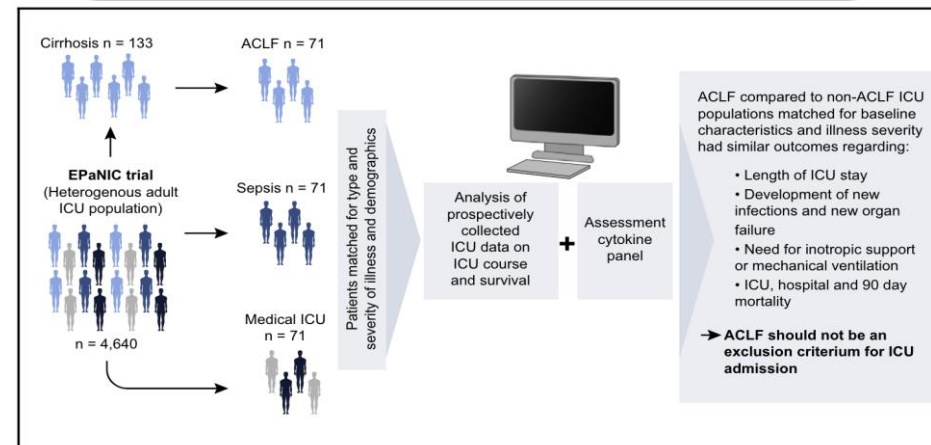
DIGESTIVO  
RAMON Y CAJAL  
MADRID

El pronóstico de los pacientes con ACLF es similar al de otros pacientes en UCI

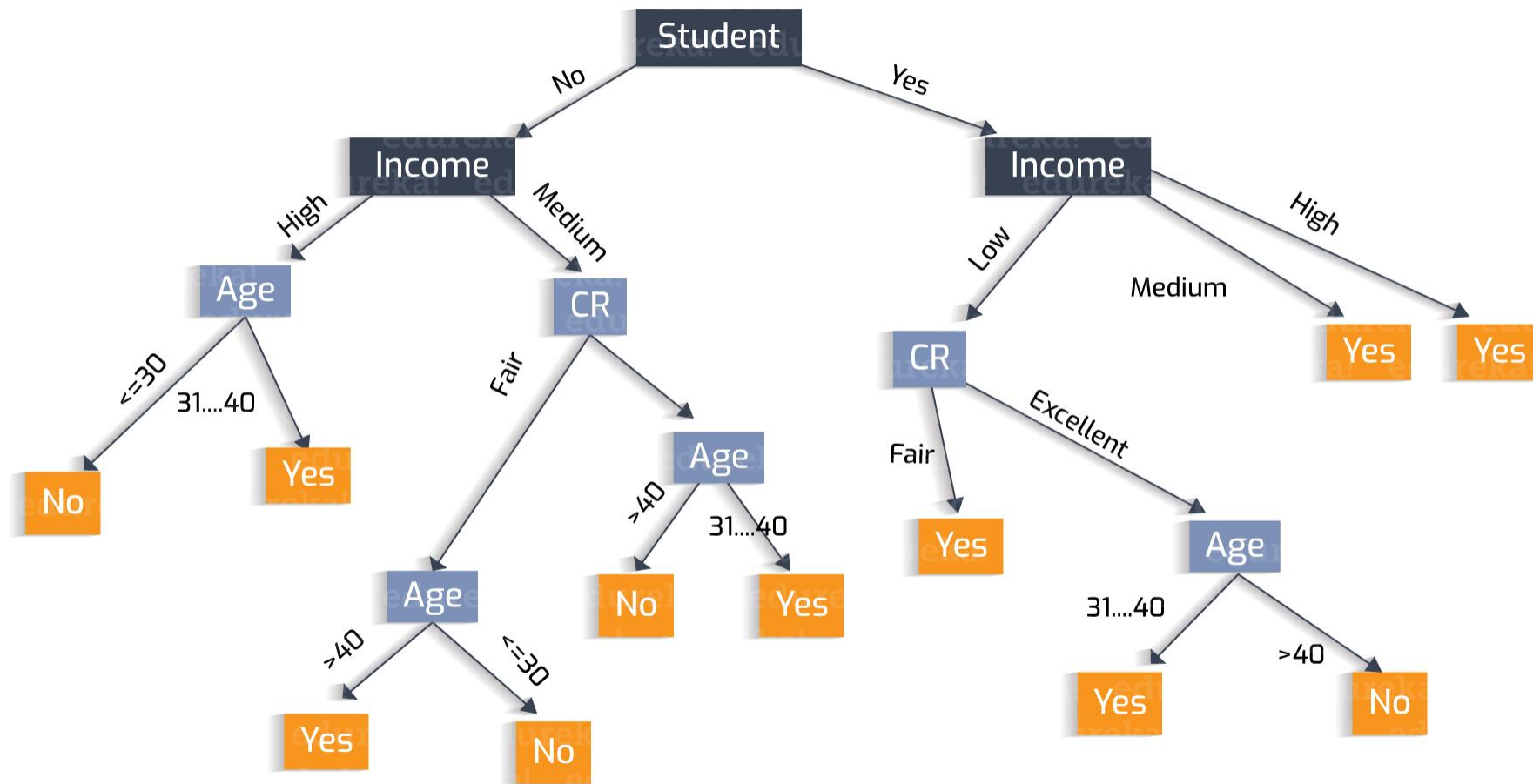


DIGESTIVO  
RAMON Y CAJAL  
MADRID

**The intensive care unit course and outcome in acute-on-chronic liver failure are comparable to other populations**



Meersseman et al. J Hepatol 2018





# MÁSTER EN HEPATOLOGÍA



Universidad Autónoma  
de Madrid



Universidad  
de Alcalá