ACLF e trapianto

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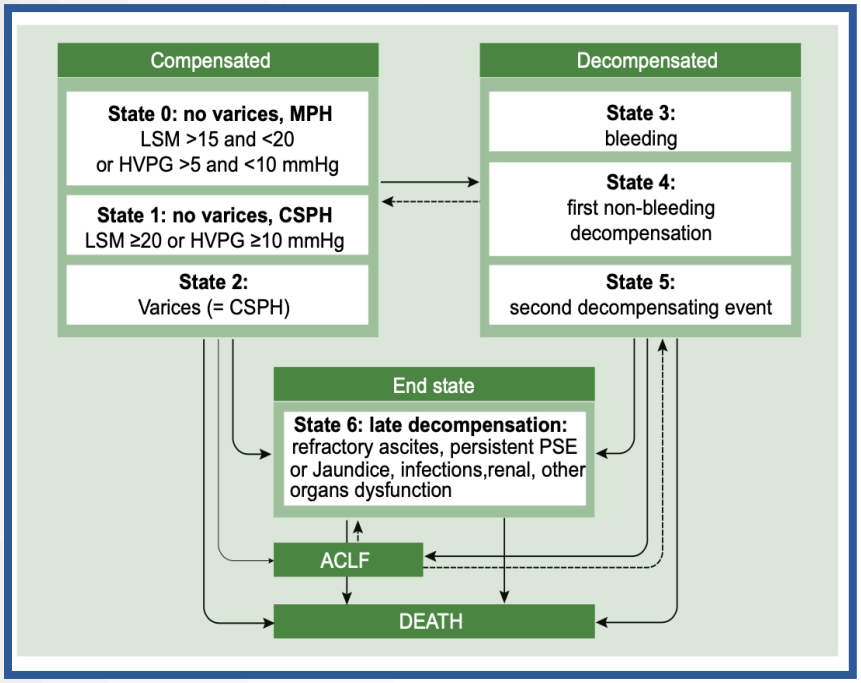
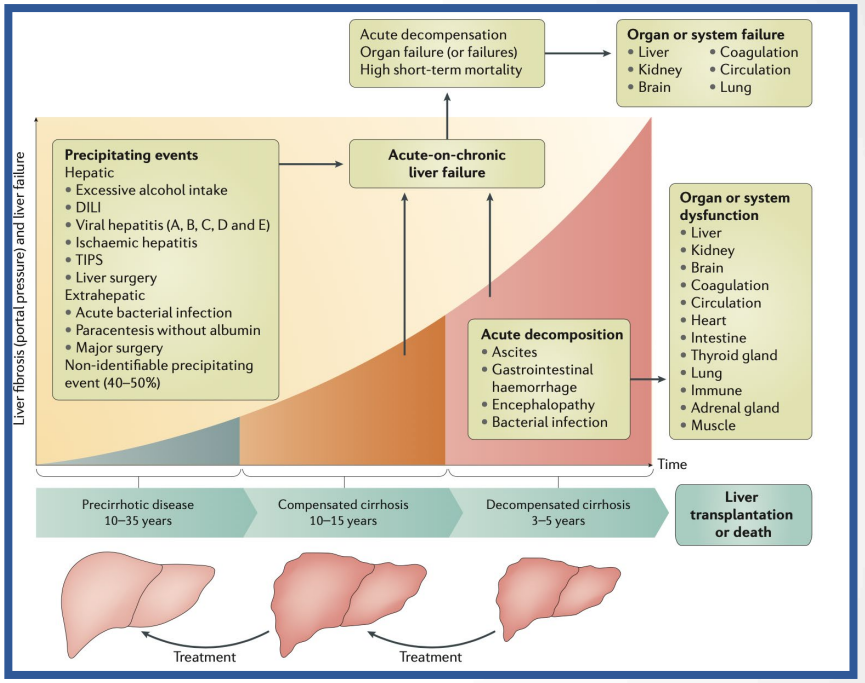
Agenda

- Definition of ACLF
- Natural history of ACLF
- The role of liver transplant in the management of ACLF

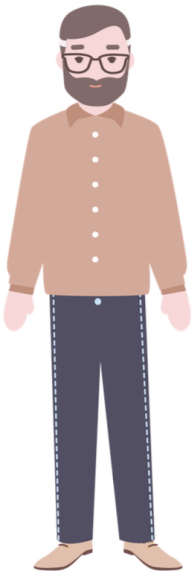


D'Amico et al, APT 2014
D'Amico et al, Journal of Hepatology 2018



Arroyo et al, Nature Reviews Disease Primers 2016

One patient's journey with decompensated cirrhosis



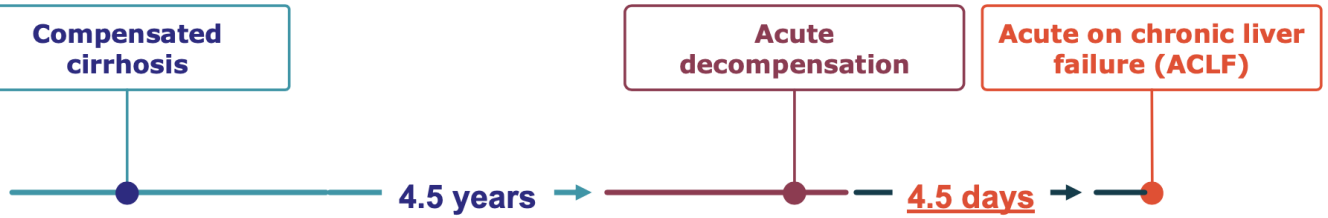
David, a 52-year old accountant, drinking 2 large glasses of wine per day diagnosed with alcoholic cirrhosis on routine health check.

No known liver disease

Admitted to hospital with **pneumonia**. On admission the patient had **fever (38ºC), leukocytosis (12.500/ml), high CRP (52 mg/L), ascites, jaundice (bilirubin 5 mg/dl).**

The patient develops hepatic encephalopathy (grade 3) and progressive jaundice (bilirubin: 16 mg/dl, INR:3) was admitted to the ICU.

He died 5 days later with progressive of liver, renal, circulatory and cerebral failure.



Courtesy of Professor Rajiv Jalan

Box 1 | **The main definitions of ACLF**

The APASL definition

For patients with compensated cirrhosis or with any kind of non-cirrhotic chronic liver disease, except isolated steatosis (definition was first made in 2004 and revised in 2014)[11,12], acute-on-chronic liver failure (ACLF) is the result of an acute direct hepatic insult (hepatotropic viral infections, active alcohol consumption or drug-induced liver injury) that causes liver failure. Liver failure is defined as jaundice (a serum bilirubin level of ≥5 mg per dl) and coagulopathy (an international normalized ratio of ≥1.5 or prothrombin activity of <40%). This liver failure is complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease (including cirrhosis). Both compensated cirrhosis and non-cirrhotic chronic liver disease (non-alcoholic fatty liver disease-related chronic hepatic injury or chronic hepatitis with fibrosis or fibrosis due to other reasons) qualify as chronic liver disease. Bacterial infections are not considered hepatic insults. Patients with cirrhosis and known prior decompensation (jaundice, encephalopathy or ascites) who develop acute deterioration of their clinical status that is either related or unrelated to precipitating events are considered to have acute decompensation but not ACLF.

The EASL-CLIF Consortium definition

For patients with cirrhosis (2013)[8], ACLF is the development of acute decompensation of cirrhosis (defined by the development of ascites, encephalopathy, gastrointestinal haemorrhage and/or bacterial infection) associated with either a single organ failure (single renal failure or other single non-renal organ failure if associated with renal and/or brain dysfunction) or multiple organ failures.

Other definitions

- Jalan and Williams definition (2002)[10]
- The Chinese Medical Association definition (2013)[15]
- The American Association for the Study of Liver Diseases and the EASL definition (2012)[14]
- North-American Consortium for the Study of End Stage Liver Disease definition (2014)[13]

APASL, Asian Pacific Association for the Study of the Liver; EASL, European Association for the Study of the Liver; EASL-CLIF, EASL-Chronic Liver Failure.

Arroyo et al, Nature Reviews Disease Primers 2016

ACLF is a specific syndrome characterized by:

- acute decompensation;
- organ failure(s);
- high short-term mortality.

AD means development of:

- ascites;
- hepatic encephalopathy;
- gastrointestinal hemorrhage;
- bacterial infections.

OFs (liver, kidney, brain, coagulation, respiration, circulation) are defined by the original CLIF-SOFA score or its simplified version CLIF-C OF score.

High short-term mortality means a 28-day mortality rate ≥15%.

Moreau R et al, Gastroenterology 2013

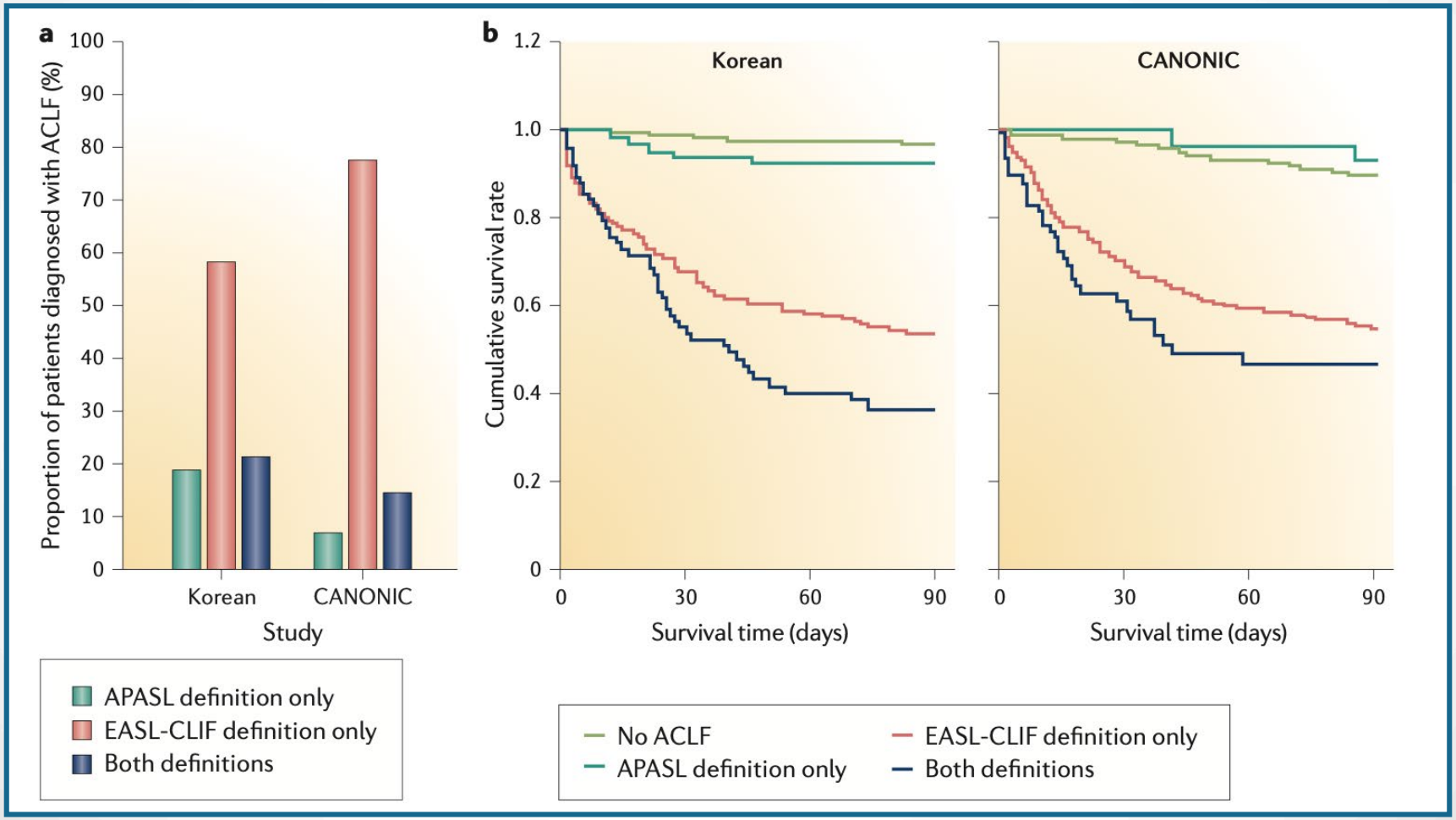
NACSELD Definition

United States and Canada

Bacterial infection-related acute decompensation of cirrhosis associated with 2 or more OFs

Kidney: need for RRT
Brain: HE grade 3-4 according to West-Haven criteria
Circulation: shock defined by MAP <60 mm Hg or a reduction of 40 mm Hg in systolic blood pressure from baseline, despite adequate fluid resuscitation
Respiratory: need for mechanical ventilation

Bajaj et al, Hepatology 2014



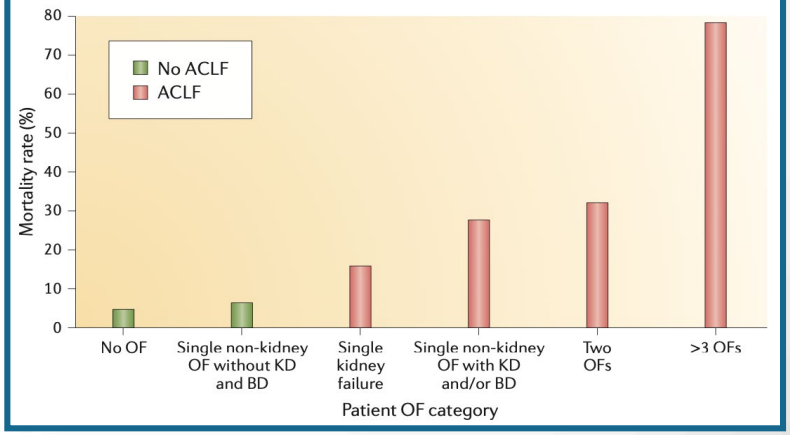
Moreau R et al, Gastroenterology 2013
Kim TY et al, PLoS ONE 2016
Arroyo et al, Nature Reviews Disease Primers 2016

Organ/system	Subscore = 1	Subscore = 2	Subscore = 3
Liver	Bilirubin <6 mg/dl	Bilirubin ≥6 mg/dl and <12 mg/dl	Bilirubin ≥12 mg/dl
Kidney	Creatinine <2 mg/dl	Creatinine ≥2 mg/dl and <3.5 mg/dl	Creatinine ≥3.5 mg/dl or renal replacement
Brain (West-Haven grade for HE*)	Grade 0	Grade 1-2	Grade 3-4**
Coagulation	INR <2.0	INR ≥2.0 and <2.5	INR ≥2.5
Circulatory	MAP ≥70 mmHg	MAP <70 mmHg	Use of vasopressors
Respiratory PaO_2/FiO_2 or SpO_2/FiO_2	 >300 or >357	 ≤300 and >200 or >214 and ≤357	 ≤200# or ≤214#

The shaded area describes criteria for diagnosing organ failures.
*HE, hepatic encephalopathy; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; SpO_2, pulse oximetric saturation.
**Patients submitted to Mechanical Ventilation (MV) due to HE and not due to a respiratory failure were considered as presenting a cerebral failure (cerebral subscore = 3).
#Other patients enroled in the study with MV were considered as presenting a respiratory failure (respiratory subscore = 3).

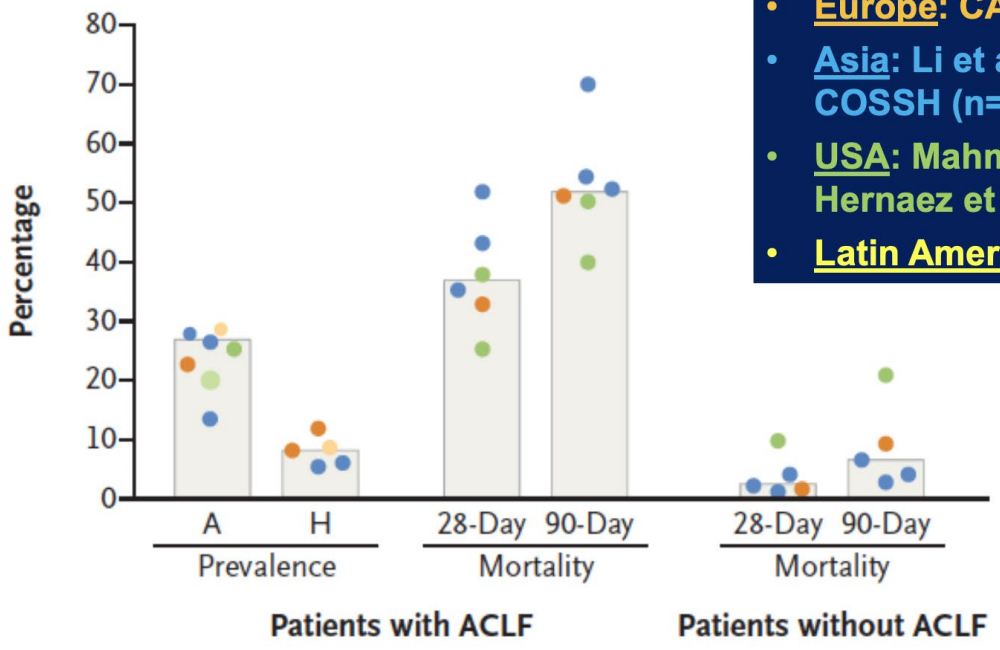
Category	28-day mortality (%)	90-day mortality (%)
No ACLF	1.9	10
ACLF (total)	33	51
ACLF grade 1	23	41
ACLF grade 2	31	55
ACLF grade 3	74	78

ACLF, acute-on-chronic liver failure. Data from REF. 8.



Moreau et al, Gastroenterology 2013
Jalan et al, Journal of Hepatology 2014
Arroyo et al, Nature Reviews Disease Primers 2016

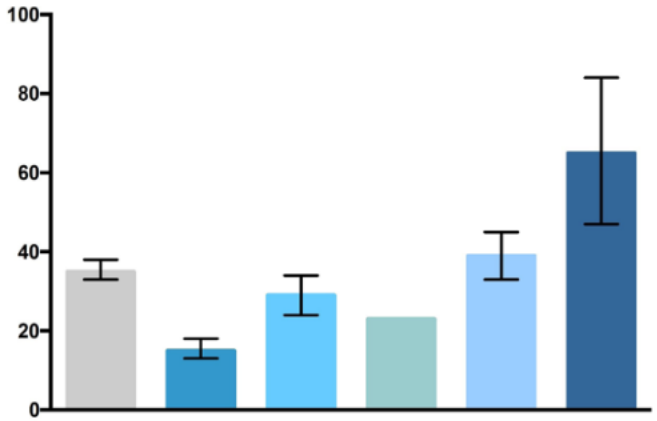
Validation of EASL-CLIF Criteria



- 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)

Arroyo, Moreau Jalan NEJM 2020

Courtesy of Professor Rajiv Jalan

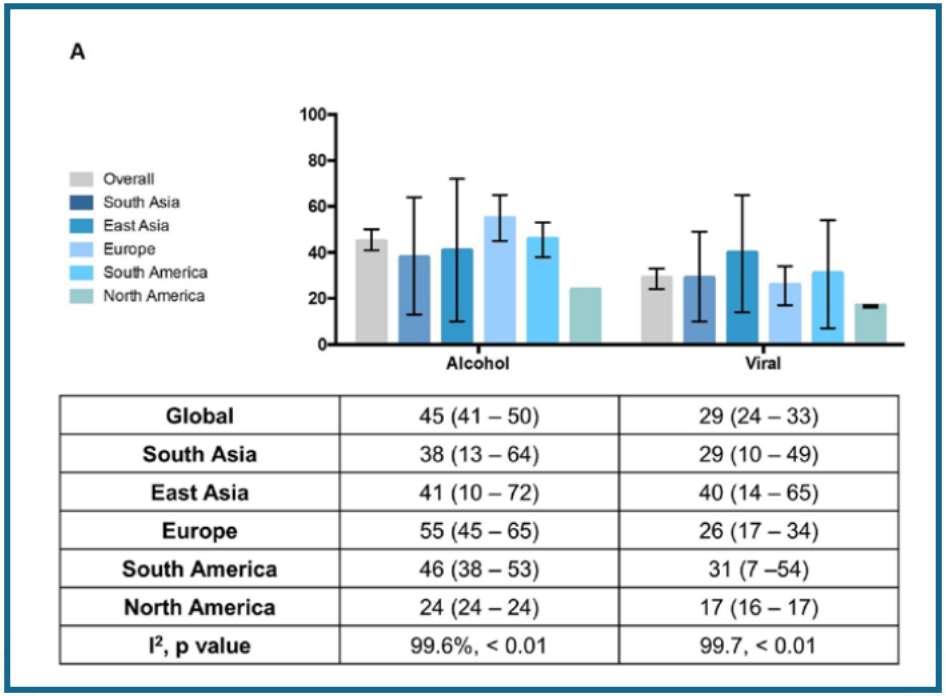


Overall	N=184,041	35 (33 - 38)
East Asia	n = 5,700	15 (13 - 18)
South America	n = 598	29 (24 - 34)
North America	n = 172,910	23 (23 – 23)
Europe	n = 4,034	39 (33 - 45)
South Asia	n = 799	65 (47 - 84)
I^2, p value		98.7%, < 0.01

Figure 1 Prevalence of acute-on-chronic liver failure (ACLF). The figure shows the global prevalence of ACLF and the prevalence of ACLF by region (Europe, North and South America, East and South Asia). Values are percentages and 95% CI.

Mezzano G, et al. Gut 2021

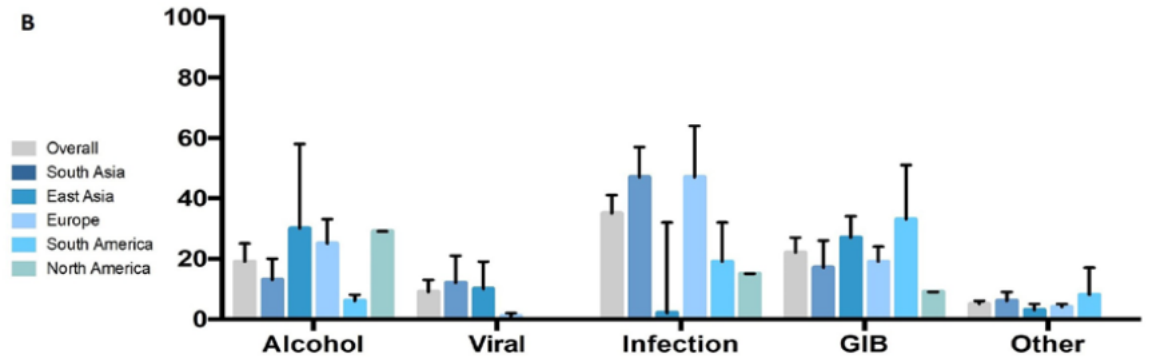
Prevalence of the aetiologies of underlying chronic liver disease worldwide and divided by region



Global	45 (41 – 50)	29 (24 – 33)
South Asia	38 (13 – 64)	29 (10 – 49)
East Asia	41 (10 – 72)	40 (14 – 65)
Europe	55 (45 – 65)	26 (17 – 34)
South America	46 (38 – 53)	31 (7 –54)
North America	24 (24 – 24)	17 (16 – 17)
I^2, p value	99.6%, < 0.01	99.7, < 0.01

Mezzano G, et al. Gut 2021

Prevalence of triggers leading to acute-on-chronic liver failure worldwide and divided by region



Global	19 (13 – 25)	9 (5 – 13)	35 (30 – 41)	22 (18 – 27)	5 (3 - 6)
South Asia	13 (6 – 20)	12 (3 – 21)	47 (36 – 57)	17 (8 – 26)	6 (3 – 9)
East Asia	30 (1 - 58)	10 (2 – 19)	2 (11 – 32)	27 (19 – 34)	3 (1 - 5)
Europe	25 (18 – 33)	1 (1 - 2)	47 (31 – 64)	19 (14 – 24)	4 (3 – 5)
South America	6 (4 – 8)	--	19 (7– 32)	33 (15 – 51)	8 (0 – 17)
North America	29 (28 – 29)	--	15 (14 – 15)	9 (8 – 9)	--
I^2, p value	99.3, < 0.01	98.4, < 0.01	99.2, < 0.01	98.5, < 0.01	92.7, < 0.01

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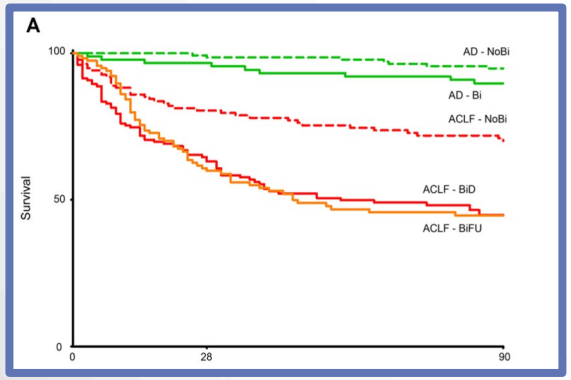
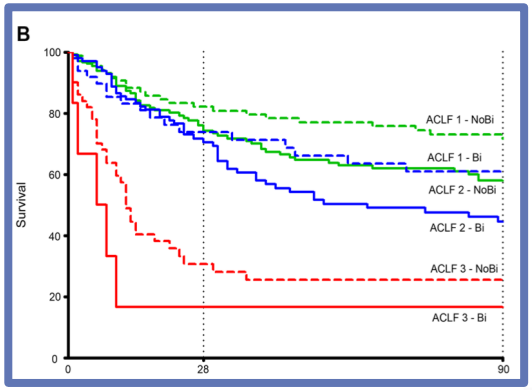
Overall impact of bacterial infections on clinical course and survival in patients with ACLF

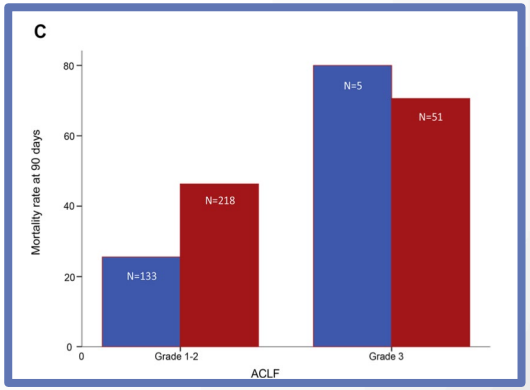
- The clinical course (**ACLF 2–3 at final assessment**: **47%** vs 26%; p<0.001) was significantly **worse** and the **probability of 90-day transplant-free survival** significantly **shorter** in patients with **ACLF and bacterial infection** (either at diagnosis or during follow-up) than in those without (45% vs 70%, p<0.001).

- **Infected patients with ACLF-1 and ACLF-2** showed a **lower 90-day probability of survival** than those without infection. In contrast, patients with ACLF-3 with and without infections did not show differences in prognosis.

- Appropriate empirical antibiotic therapy was administered in 74% and 72% of bacterial infections triggering and complicating ACLF, respectively.
- **Adequacy** of **initial antibiotic strategies** was associated with **lower critical care requirements**, **better evolution** of the syndrome in infection-triggered ACLF and **lower 28- and 90-day mortality**.







Fernández J, *et al*. *Gut* 2018;**67**:1870–1880. doi:10.1136/gutjnl-2017-314240

Fungal infection and colonisation

- Fungal isolation was infrequent and mainly observed in patients with ACLF (3.9% vs 0.4%, p=0.005).
- Of the 16 patients with ACLF and fungal isolation, **7** corresponded to **invasive candidiasis** (five candidemias and two secondary peritonitis), **1** to **probable IA** and 8 to colonisation by Candida.

- **6** out of the 8 **invasive fungal infections** were diagnosed **during follow-up** in patients with ACLF. In the remaining two patients (a secondary peritonitis and an IA), diagnosis was performed at ACLF diagnosis.

- **Mortality rates** associated with **invasive fungal infection** and colonisation were **57%** and 44% at **28 day** and **71%** and 67% at **90 day**, respectively.

Fernández J, *et al*. *Gut* 2018;**67**:1870–1880. doi:10.1136/gutjnl-2017-314240

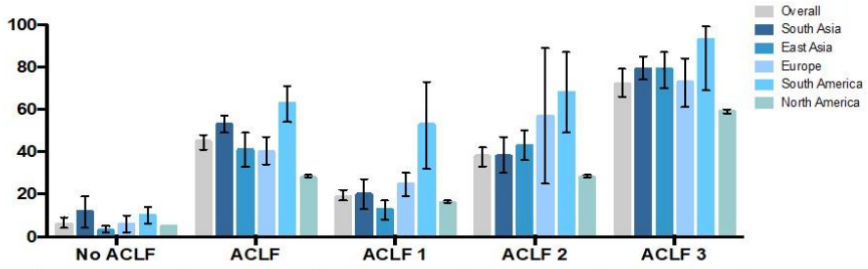
- **MDR bacteria** were more frequently **isolated** in the **ICU** and in **nosocomial episodes**.
- **MDR bacterial infections** were more severe (**higher rate** of **severe sepsis/shock** and/or **ACLF** at diagnosis) and associated to **lower resolution rate** and **higher mortality at 28 days**, especially if treated with inadequate empirical antibiotic strategies.

- A **nosocomial origin** of infection, **ICU admission** and **recent hospitalization** within the previous 3 months were the only **independent risk factors** for **MDR bacterial infections** identified in the whole CANONIC cohort.

- Inadequacy of first-line antibiotic strategies had a negative impact on short-term survival, both in patients with AD and ACLF, a feature also observed when the analysis was restricted to MDR bacterial infections.
- Broad schemes covering all potential pathogens should be empirically used in the nosocomial setting and in severe sepsis/shock and should be followed by rapid de-escalation strategies to avoid a further spread of antibiotic resistance.

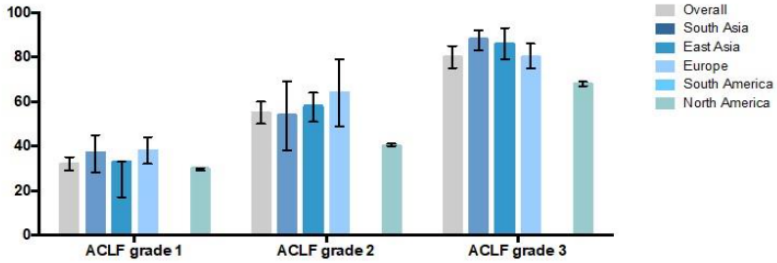
Fernendéz J et al, Journal of Hepatology 2019

28-day mortality



Global	6 (4 – 9)	45 (41 – 48)	19 (17 – 22)	38 (33 – 42)	72 (66 – 79)
South Asia	12 (4 – 19)	53 (49 – 57)	20 (13 – 27)	38 (30 – 47)	79 (74 – 85)
East Asia	3 (2 – 5)	41 (33 – 49)	13 (8 – 17)	43 (36 – 50)	79 (70 – 87)
Europe	6 (2 – 10)	40 (34 – 47)	25 (19 – 30)	57 (25 – 89)	73 (61 – 84)
South America	10 (6 – 14)	63 (54 – 71)	53 (32 – 73)	68 (49 – 87)	93 (69 – 99)
North America	5 (5 – 5)	28 (28 – 29)	16 (16 – 17)	28 (28 – 29)	59 (58 – 60)
I^2, p value	99.4, < 0.01	98.3, < 0.01	97.3, < 0.01	87.7, < 0.01	92.6, < 0.01

90-day mortality



Global	32 (29 – 35)	55 (50 – 60)	80 (75 – 85)
South Asia	37 (28 – 45)	54 (38 – 69)	88 (83 – 92)
East Asia	23 (17 – 29)	58 (51 – 64)	86 (79 – 93)
Europe	37 (31 – 44)	66 (50 – 83)	81 (75 – 87)
South America	--	--	--
North America	30 (29 – 30)	40 (40 – 41)	68 (67 – 69)
I^2, p value	75.2, < 0.01	98.8, < 0.01	99.3, < 0.01

Mezzano G, et al. Gut 2021

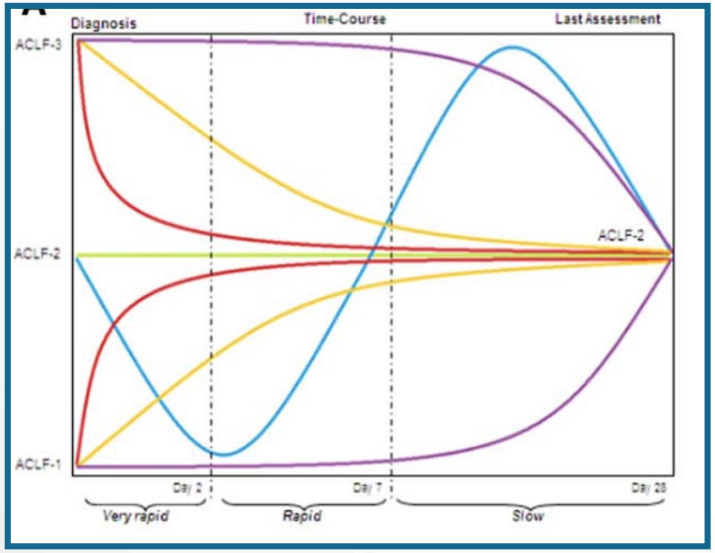
Agenda

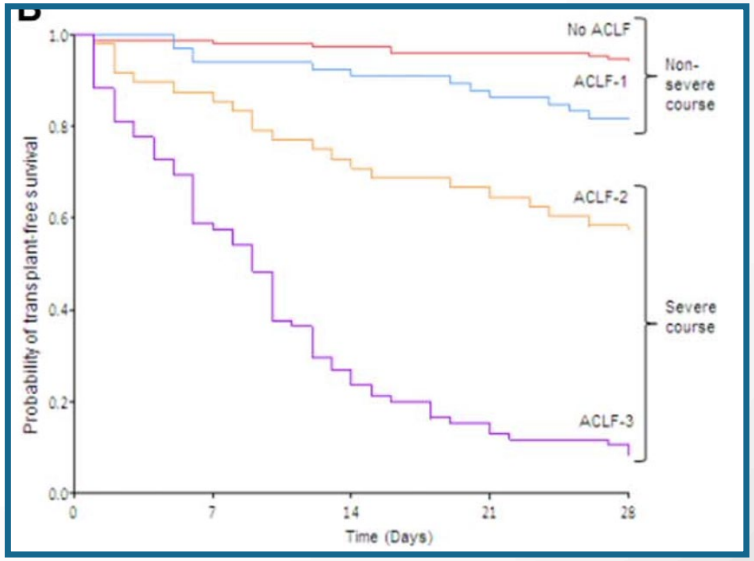
- Definition of ACLF
- Natural history of ACLF
- The role of liver transplant in the management of ACLF

Table 1. Clinical Course Patterns and Types in Those Patients With ACLF Studied*

Initial Grade	Final Grade			
	No ACLF (n = 165)	ACLF-1 (n = 70)	ACLF-2 (n = 59)	ACLF-3 (n = 94)
ACLF-1 (%)				
Prevalence (n = 202)	110 (54.5)	49 (24.3)	18 (8.9)	25 (12.4)
28-day tx-free mortality (n = 190)	7/104 (6.7)	10/47 (21.3)	8/15 (53.3)	21/24 (87.5)
90-day tx-free mortality (n = 172)	19/95 (20.0)	17/41 (41.5)	10/13 (76.9)	23/23 (100)
ACLF-2 (%)				
Prevalence (n = 136)	47 (34.6)	19 (14.0)	35 (25.7)	35 (25.7)
28-day tx-free mortality (n = 118)	1/42 (2.4)	2/17 (11.8)	8/27 (29.6)	29/32 (90.63)
90-day tx-free mortality (n = 110)	5/39 (12.8)	5/16 (31.3)	18/23 (78.3)	32/32 (100)
ACLF-3 (%)				
Prevalence (n = 50)	8 (16.0)	2 (4.0)	6 (12)	34 (68)
28-day tx-free mortality (n = 45)	1/8 (12.5)	0/2 (0.0)	4/6 (66.7)	28/29 (96.6)
90-day tx-free mortality (n = 45)	1/8 (12.5)	1/2 (50.0)	4/6 (66.7)	28/29 (96.6)

ACLF: resolution or improvement (green boxes); steady *or* fluctuating course with unchanged final ACLF grade (uncolored boxes); and worsening (red boxes).
*Prevalence and associated 28- and 90-day transplant (tx)-free mortality.





Gustot et al, Hepatology 2015

The CLIF-C ACLF score

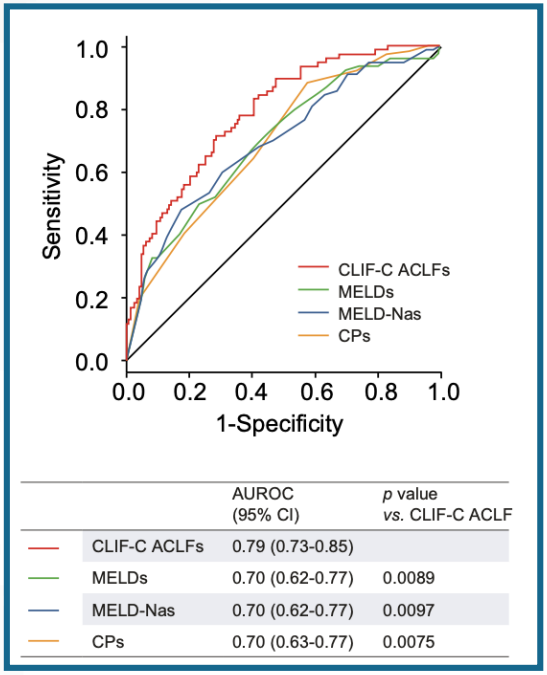
CLIF-C ACLF score = 10 x [0.33 x CLIF-OFs + 0.04 x Age + 0.63 x Ln (WBC count) – 2]

The cumulative probability of death at time "t" can be estimate by the equation:

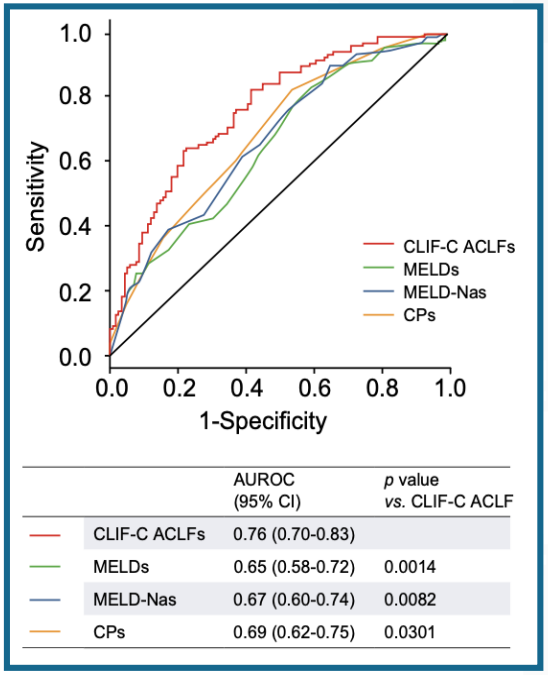
$$P = 1 - e^{-Cl(t) \times \exp[\beta(t) \times \text{Clif-C-ACLF score}]}$$

Jalan et al, Journal of Hepatology 2014

The score can be calculated at the European Foundation for the study of Chronic Liver Failure (EF-CLIF) website http://www.efclif.com



	AUROC (95% CI)	*p* value *vs.* CLIF-C ACLF
CLIF-C ACLFs	0.79 (0.73-0.85)	
MELDs	0.70 (0.62-0.77)	0.0089
MELD-Nas	0.70 (0.62-0.77)	0.0097
CPs	0.70 (0.63-0.77)	0.0075



	AUROC (95% CI)	*p* value *vs.* CLIF-C ACLF
CLIF-C ACLFs	0.76 (0.70-0.83)	
MELDs	0.65 (0.58-0.72)	0.0014
MELD-Nas	0.67 (0.60-0.74)	0.0082
CPs	0.69 (0.62-0.75)	0.0301

	28-day mortality				90-day mortality			
	CLIF-C ACLF score		MELD score		CLIF-C ACLF score		MELD score	
	C-index (95% CI)	*p* value *vs.* baseline	C-index (95% CI)	*p* value *vs.* baseline	C-index (95% CI)	*p* value *vs.* baseline	C-index (95% CI)	*p* value *vs.* baseline
CLIF-C-ACLF score at enrolment (N = 256)	0.751 (0.701-0.800)		0.679 (0.621-0.737)		0.712 (0.666-0.759)		0.653 (0.602-0.703)	
CLIF-C-ACLF score at 48 hours (N = 186)	0.801 (0.747-0.854)	0.0956	0.721 (0.658-0.783)	0.1890	0.751 (0.700-0.802)	0.1336	0.680 (0.625-0.736)	0.3312
CLIF-C-ACLF score at 3-7 days (N = 189)	0.822 (0.767-0.877)	0.0179	0.749 (0.682-0.815)	0.0389	0.774 (0.722-0.827)	0.0217	0.706 (0.646-0.765)	0.0824
CLIF-C-ACLF score at 8-15 days (N = 154)	0.866 (0.809-0.923)	0.0001	0.799 (0.729-0.870)	0.0008	0.790 (0.733-0.847)	0.0072	0.710 (0.643-0.776)	0.0958

**p* value *vs.* CLIF-C score at enrolment.

Jalan et al, Journal of Hepatology 2014

Table 3. AARC score and ACLF grading system.

AARC score					
Points	**Total bilirubin (mg/dl)**	**HE grade**	**INR**	**Lactate (mmol/L)**	**Creatinine (mg/dl)**
1	<15	0	<1.8	<1.5	<0.7
2	15–25	I–II	1.8–2.5	1.5–2.5	0.7–1.5
3	>25	III–IV	>2.5	>2.5	>1.5

AARC ACLF grade		
Grade	**Points**	**28-day mortality rates (%)**
I	5–7	12.7
II	8–10	44.5
III	11–15	85.9

AARC score (adapted from [14]). AARC, APASL ACLF Research Consortium; ACLF, acute-on-chronic liver failure; APASL, the Asian Pacific Association for the Study of the Liver; HE, hepatic encephalopathy; INR, international normalized ratio.

Choudhury A et al, Hepatol Int 2017

The score can be calculated at AARC website
http://www.aclf.in/ ?page=doctor_aarc_grade_cal

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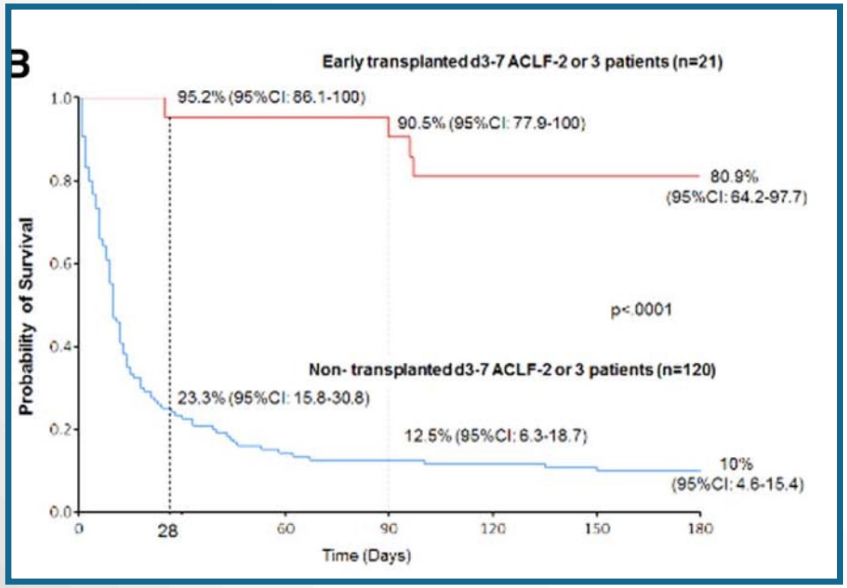
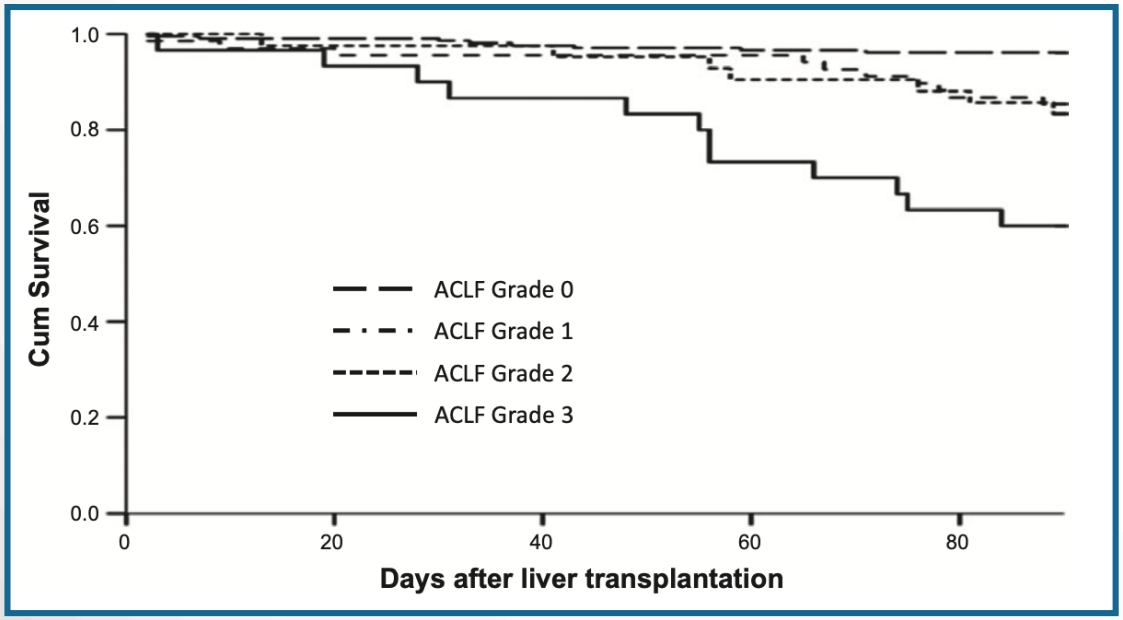
- Definition of ACLF
- Natural history of ACLF
- The role of liver transplant in the management of ACLF

Study	Experience	Criteria for ACLF diagnosis	Number of LT	Survival post-LT	Notes
Gustot T et al. 2015	CANONIC Europe 29 centers	CLIF-C criteria	35 pts with initial ACLF: - 25 pts with ACLF at LT (ACLF-1, 5; ACLF-2, 11; ACLF-3, 9) ▪ Mean MELDs 34 and mean CLIF-C ACLFs 50.3 ▪ Renal failure 64%, coagulation failure 60%, liver failure 56%, circulatory failure 36%, cerebral failure 22%, respiratory failure 0% ▪ Vasoactive agents 52%, RRT 40% and MV 28% - 10 pts with ACLF resolution at LT ▪ Mean MELDs 25.8 ▪ Liver failure 60%, coagulation failure 10% ▪ Vasoactive agents 50%, MV 10%	1-year: - pts with ACLF at LT: 75.3% (ACLF-1, 80%; ACLF-2, 71.6%; ACLF-3, 77.8%) - pts with ACLF resolution before LT: 90%	DDLT LT within 28 days (median time between ACLF diagnosis and LT 11 days) 6-month probability of survival of d3-7 ACLF-2 or -3 pts undergoing LT compared to LT-free survival probability in d3-7 ACLF-2 or -3 pts: 80.9% vs 10%



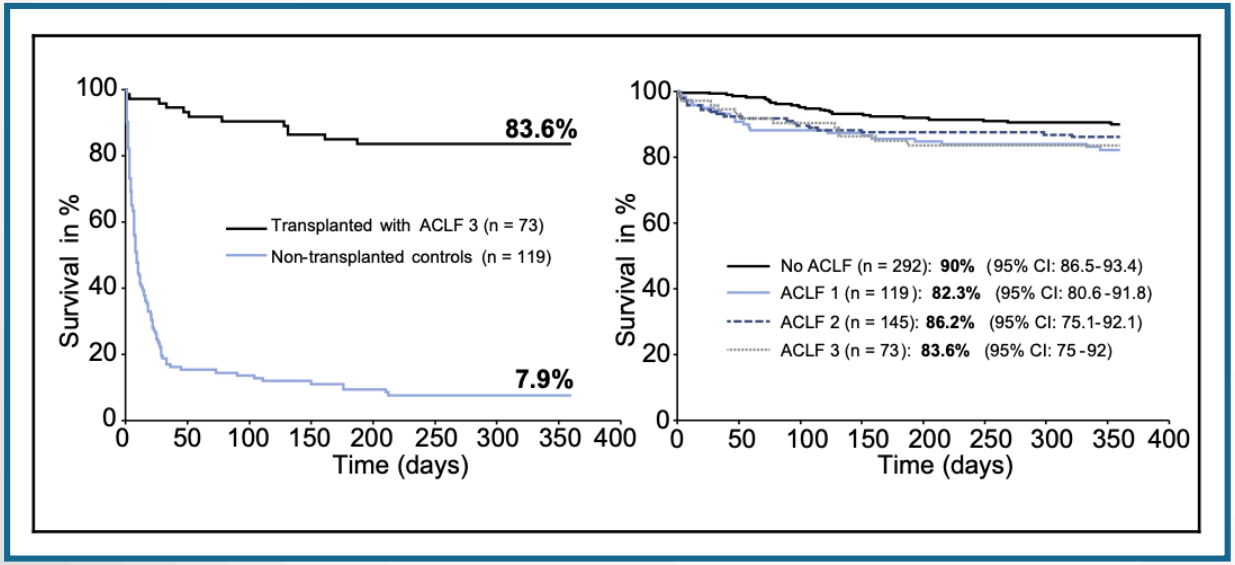
Gustot T et al, Hepatology 2015; 62: 243-252

Study	Experience	Criteria for ACLF diagnosis	Number of LT	Survival post-LT	Notes
Levesque E et al. 2017	France 1 centre	CLIF-C criteria	140 pts with ACLF at LT with a mean MELDs 29.5 and a mean CLIF-SOFAs 10.3 - ACLF-1, 68 pts - ACLF-2, 42 pts - ACLF-3, 30 pts (3-OFs 10 pts, ≥4 OFs 20 pts) Coagulation failure 65%, liver failure 53.6%, renal failure 19.3%, cerebral failure 23.6%, respiratory failure 20.7%, circulatory failure 17% RRT 11%	1-year: 70% (ACLF-1 or -2, 77.2%; ACLF-3, 43.3%)	DDLT Mean post-LT ICU and hospital stays: 17.5 and 47.5 days 1-year survival post-LT in 210 pts without ACLF: 91.4%



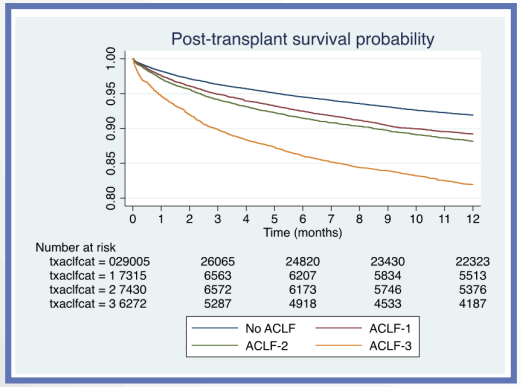
Levesque et al, Liver International 2017

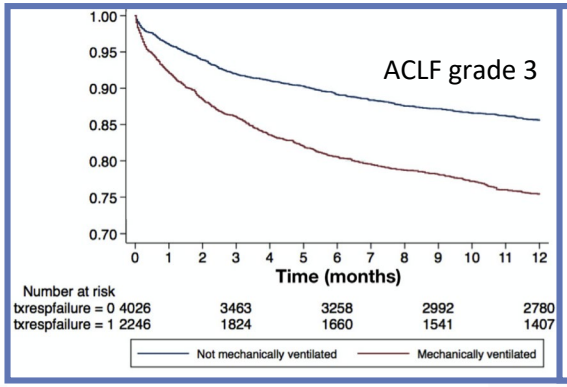
Study	Experience	Criteria for ACLF diagnosis	Number of LT	Survival post-LT	Notes
Artru F et al. 2017	France 3 centers	CLIF-C criteria	73 pts with ACLF-3 with median MELDs and CLIF-C ACLFs at LT 40 and 63.5, respectively - MV 46 pts - Noradrenalin, median dose 0.5 mg/h, 45 pts - RRT 34 pts	1-year: 83.6%	DDLT Absolute contraindications to LT: active gastrointestinal bleeding, control of sepsis <24 h, hemodynamic instability requiring dose of noradrenalin >3 mg/h, severe ARDS (PaO2/FiO2 <150) Median pre-LT ICU stay 9 days (5-14) and median time between placement on WL and LT 8 days (3-24) Median post-LT ICU stay 18 days (10-33.5) and median total hospital stay 51 days (37-79.8) 100% pts with ACLF-3 developed complications 1-year survival of 119 non-LT controls: 7.9% 1-year survival of controls without ACLF (292 pts), with ACLF-1 (119 pts), and with ACLF-2 (145 pts): 90%, 82.3%, and 86.2%

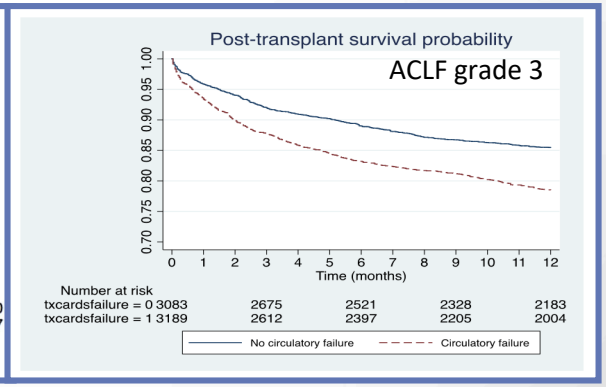


Artru et al, J. Hepatol. 2017; 67 : 798-715

Study	Experience	Criteria for ACLF diagnosis	Number of LT	Survival post-LT	Notes
Sundaram V et al. 2019	UNOS registry	CLIF-C criteria	7375 pts with ACLF-1 7513 with ACLF-2 6381 with ACLF-3 - 3 OFs 3583 pts - 4 OFs 1646 pts - 5 OFs 866 pts - 6 OFs 286 pts	1-year: - No ACLF, 91.9% - ACLF-1, 89.1% - ACLF-2, 88.1% - ACLF-3, 81.8% ▪ MV: 75.3%% ▪ No MV: 85.4% ▪ Circulatory failure: 78.4% ▪ No circulatory failure: 85.3% ▪ KPS <80%: 81.8% ▪ KPS ≥80%: 88.5% ▪ DRI ≥1.7: 78.1% ▪ DRI <1.7: 82.9% ▪ FRS >8: 74.7% ▪ FRS ≤8: 84.4% ▪ LT after 30 days: 79.4% ▪ LT within 30 days: 82.5%	Death or WL removal within 90 days of transplant listing - No ACLF ▪ MELD-Na <25: 16.1% ▪ MELD-Na 25-29: 19.9% ▪ MELD-Na 30-34: 21.2% ▪ MELD-Na ≥35: 21.2% - ACLF-1 ▪ MELD-Na <25: 19.9% ▪ MELD-Na 25-29: 21.8% ▪ MELD-Na 30-34: 21.1% ▪ MELD-Na ≥35: 22.7% - ACLF-2 ▪ MELD-Na <25: 30.9% ▪ MELD-Na 25-29: 20.7% ▪ MELD-Na 30-34: 18.9% ▪ MELD-Na ≥35: 22% - ACLF-3 ▪ MELD-Na <25: 43.8% ▪ MELD-Na 25-29: 36.9% ▪ MELD-Na 30-34: 29.9% ▪ MELD-Na ≥35: 35.2%







Sundaram et al, Gastroenterology 2019

Study	Experience	Criteria for ACLF diagnosis	Number of LT	Survival post-LT	Notes
Moon DB et al. 2017	Korea 1 center	CLIF-C criteria	190 pts with ACLF and MELDs ≥30 (mean MELDs 38.4) - ACLF-1, 96 pts - ACLF-2, 43 pts - ACLF-3, 51 pts	1-, 3-, and 5-year patient survival: 79.5%, 73.6%, and 72.1%	LDLT Hospital mortality: 15.8% Frequency of total complications: 74.7% 1-, 3-, and 5-year graft survival: 76.8%, 72.1%, and 70.5% 1-, 3-, and 5-year patient survival of 137 non-ACLF pts with MELDs ≥30: 90.5%, 83.2%, and 81.8%

Study	Experience	Criteria for ACLF diagnosis	Number of LT	Survival post-LT	Notes
Huebener P et al. 2018	Germany 1 center	CLIF-C criteria	98 pts with ACLF within 3 months prior to LT At diagnosis - ACLF-1, 24 pts - ACLF-2, 45 pts - ACLF-3, 29 pts Median MELDs at LT 34.5 37 pts experienced recovery of at least 1 OF(s) before LT	3-month survival: 72.4% - ACLF-1, 84.2% - ACLF-2, 75% - ACLF-3, 66% 2-year survival: 60.2%	Median ICU and hospital stay post-LT: 16 and 45 days 3-month, and 2-year survival of 152 non-ACLF pts: 96.1%, 86.8% 90-day patients and graft survival rates identical between ACLF improvers and non-ACLF LT recipients.
Bhatti ABH et al. 2018	Pakistan 1 center	CLIF-C criteria	60 pts with a median MELDs 29 - ACLF-1, 43 pts - ACLF-2, 15 pts - ACLF-3, 2 pts	1-year overall survival: 92% - ACLF-1, 91% - ACLF-2, 93% - ACLF-3, 100%	LDLT 1-year overall survival in 59 ACLF pts non-receiving LT: 11%
Thuluvath PJ et al. 2018	UNOS	CLIF-C criteria	Pts who were transplanted within 30 days of listing - No OF 7881 pts with a mean MELDs 16 - 1 OF 4330 pts with a mean MELDs 27 - 2 OFs 3557 pts with a mean MELDs 34 - 3 OFs 1947 pts with a mean MELDs 39 - 4 OFs 932 pts with a mean MELDs 39 - 5-6 OFs 677 pts with a mean MELDs 40	1-year survival - No OF 90% - 1 OF 88% - 2 OFs 88% - 3 OFs 84% - 4 OFs 81% - 5-6 OFs 81% 5-year survival - No OF 74% - 1 OF 74% - 2 OFs 74% - 3 OFs 73% - 4 OFs 67% - 5-6 OFs 67%	LT median time 4-5 days in pts with ≥3 OFs 30-day removal from the list because death or LT - No OF 10% - 1 OF 45% - 2 OFs 80% - 3 OFs 92% - 4 OFs 94% - 5-6 OFs 98%

Study	Experience	Criteria for ACLF diagnosis	Number of LT	Survival post-LT	Notes
Yadav SK et al. 2019	India 1 center	CLIF-C criteria	117 pts with a mean MELDs 30.6 and a mean CLIF-C ACLFs 46.9 - ACLF-1, 28 pts - ACLF-2, 48 pts - ACLF-3, 41 pts	1-year survival - ACLF-1, 92.9% - ACLF-2, 85.4% - ACLF-3, 75.6%	Entire study cohort: 218 pts (ACLF-1, 35; ACLF-2, 66; ACLF-3, 117). Underwent to LT: ACLF-1, 80%; ACLF-2, 72.7%; ACLF-3, 35% LDLT Absolute contraindications to LT: circulatory failure (high dose inotropes), respiratory failure (MV), renal failure (HD) Post-LT morbidity: sepsis 41% Mortality without LT at 3 months: ACLF-1, 28.5%; ACLF-2, 77.7%; ACLF-3, 93.4%

Study	Experience	Criteria for ACLF diagnosis	Number of LT	Survival post-LT	Notes
Chan AC et al. 2009	China 1 center	APASL criteria	149 pts with ACLF divided in 2 subgroups - Acute exacerbation of chronic hepatitis B: 50 pts, median MELDs 37 - Cirrhosis with acute deterioration: 99 pts, median MELDs 35 HRS 57 pts, pre-LT HD 28, MV 43 pts	1-, 3-, and 5-year overall survival rates: 96% and 95%, 96% and 90.5%, 93.2% and 90.5%	DDLT 46 pts, LDLT 103 pts Hospital mortality: 4% and 5.1% Early complications (<30 days): 62% and 70.7% Post-LT HD: 10% and 11.1% Median ICU stay: 6 (1-37) and 5 (1-125) days Median hospital stay: 18 (10-79) and 24 (8-210) days 5-year overall survival post-LT of 301 cirrhotic pts: 79.3%
Chen Z et al. 2011	China 1 center	Chronic pre-existing HBV, serum bilirubin >20 mg/dL and/or HE grade >2	19 pts with HBV ACLF with a mean MELDs 39.8	1-, 6-, and 12-month survival rates: 88.89%, 83.33%, and 83.33%	LDLT Survival of 28 pts with HBV ACLF not undergoing LDLT <3 months 1-, 6-, and 12-month post-LT survival of 30 pts without ACLF: 96.67%, 93.33% and 93.33%
Bahirwani R et al. 2011	USA 1 center	Rise in MELDs >5 points within 4 weeks before LT	157 pts with ACLF with a mean MELDs al LT 28.77	Survival rate after a median follow-up of 4.67 years: 74.5%	45% of deaths post-LT in ACLF pts were liver-related Post-LT survival rate in 175 non-ACLF pts after a median follow-up of 3.82 years: 83.4%

Study	Experience	Criteria for ACLF diagnosis	Number of LT	Survival post-LT	Notes
Ling Q et al 2012	China 1 center	APASL criteria	126 pts with HBV ACLF and MELDs ≥30 at listing - emergency LT (ELT group) 42 pts - ALSS with MELD <30 at LT (DGM group) 33 pts - ALSS with MELD ≥30 at LT (N-DGM group) 51 pts	Overall survival after a median of 1.53 (0.03-9.86) years follow-up - ELT group: 83.3% - DGM group: 84.8% - N-DGM group: 56.9%	DDLT 93 pts, LDLT 33 pts Early (<30 days) mortality - ELT group: 14.3% - DGM group: 9.1% - N-DGM group: 23.5%
Xing T et al. 2013	China 1 center	APASL criteria	133 pts with HBV ACLF - 103 pts without renal dysfunction (median MELDs 21.3): only LT - 18 pts with HRS-1 (median MELDs 33.6): only LT - 12 pts with ESRD (median MELDs 32.1): CLKT	1-, 3-, and 5-year overall survival rates: - pts without renal dysfunction: 75.7%, 73.8%, and 72.8% - pts with HRS-1: 61.1%, 61.1%, and 61.1% - pts with ESRD: 100%, 83.3%, and 83.3%	DDLT Hospital mortality: - pts without renal dysfunction: 20.4% - pts with HRS-1: 44.4% - pts with ESRD: 0% Early (<30 days) complications: - pts without renal dysfunction: 13.6% - pts with HRS-1: 27.8% - pts with ESRD: 8.3%
Duan BW et al. 2013	China 1 center	EASL–AASLD consensus working definition + SOFAs	100 pts with ACLF with a median MELDs 32 (19-53) and a median SOFAs 9 (6-20) - MV 7 pts - HRS 25 pts - Cerebral failure 20 pts	1-, 3-, and 5-year cumulative survival rates: 76.8%, 75.6%, and 74.1%	DDLT 84 pts, LDLT 16 pts Overall hospital mortality: 20% Early (<30 days) complications: 41% Median hospital stay 45 days (8-170) 1-, 3-, and 5-year cumulative graft survival rates: 73.3%, 72.1%, and 70.6%

Study	Experience	Criteria for ACLF diagnosis	Number of LT	Survival post-LT	Notes
Finkenstedt A et al. 2013	Austria 1 center	APASL criteria	33 pts with ACLF with a median MELDs 27 (17-38)	Overall survival after a mean follow-up of 29 (2-85) months: 85% 3-month, 1-year, and 5-year survival rates: 94%, 87%, and 82%	Median overall survival and transplant-free survival times of the entire ACLF cohort (144 pts): 54 and 48 days Only 10 pts out of 144 (ACLF cohort) survived without LT with a median follow-up of 1.5 years DDLT WL mortality: 54% Probability of death on WL: 37% after 1 month, 52% after 3 months Median waiting time for LT: 24 (5-115) days 3-month, 1-year, and 5-year survival rates in non-ACLF cohort: 98%, 93%, and 82%
Lin KH et al 2013	Taiwan 1 center	APASL criteria	54 pts with ACLF - pre-LT infection (group 1) 34 pts - no pre-LT infection (group 2) 20 pts with a median MELDs 24	1-year patient survival: - group 1, 94.1% - group 2, 90%	LDLT 1-year graft survival: - group 1, 94.1% - group 2, 90%
O'Leary JG et al. 2019	North America 14 centers	NACSELD criteria	57 pts having experienced an episode of ACLF during index admission and with median MELDs at LT 31.1	3- and 6-month survival: 94% and 93%	DDLD and LDLT Median time to LT: 27 days 3- and 6-month survival of transplanted pts without ACLF: 96% and 93%

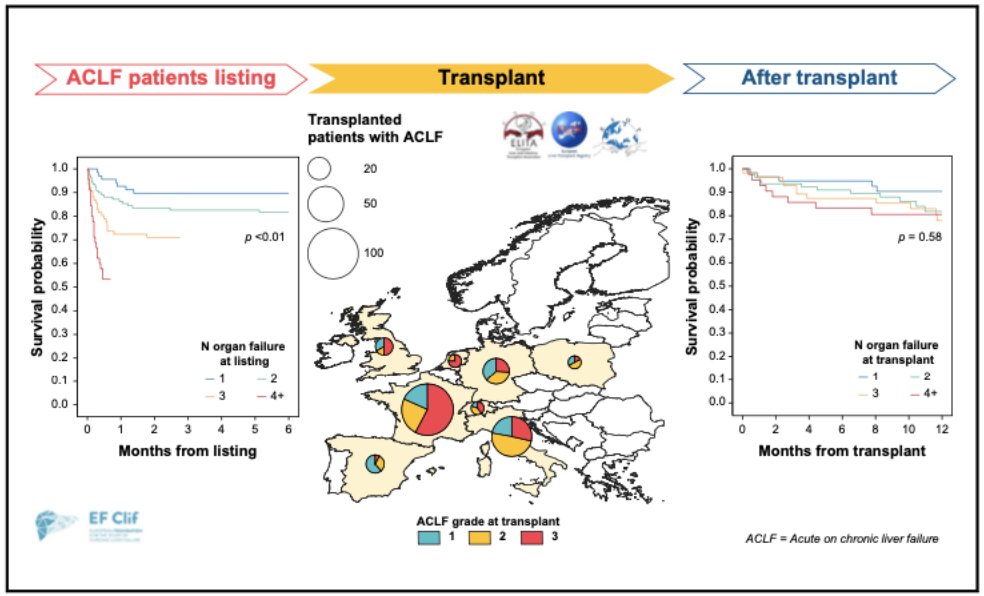
Research Article
Liver Transplantation

JOURNAL OF HEPATOLOGY

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

Journal of Hepatology **2021** vol. 75 | 610–622

Graphical abstract



- How many **patients with ACLF** were **listed** and **received a LT** between January 2018 and June 2019 across Europe and how does practice vary between countries?
- What were **survival rates** after listing for LT and after LT?
- What were the **determinants** of **mortality** in both settings?

Patients with ACLF at listing or occurring after listing

Baseline characteristics

	ACLF at listing or at occurrence (if after listing)			Total (N=308)
	ACLF-1 (N=68)	ACLF-2 (N=109)	ACLF-3 (N=131)	
ACLF grade at listing[abc]				
No ACLF (incident cases)	19 (27.94%)	22 (20.18%)	40 (30.53%)	81 (26.30%)
1	49 (72.06%)	-	-	49 (15.91%)
2	-	87 (79.82%)	-	87 (28.25%)
3	-	-	91 (69.47%)	91 (29.55%)
Patients developing ACLF after listing (incident cases)	19 (27.94%)	22 (20.18%)	40 (30.53%)	81 (26.30%)
Number of organ failure[abc]				
1	68 (100.00%)	-	-	68 (22.08%)
2	-	109 (100.00%)	-	109 (35.39%)
3	-	-	76 (58.02%)	76 (24.68%)
4+	-	-	45 (34.35%)	45 (14.61%)
Missing	0 (0.00%)	0 (0.00%)	10 (7.63%)	10 (3.25%)
Type of organ failure				
Liver failure	55 (80.88%)	95 (87.16%)	102 (77.86%)	252 (81.82%)
Renal failure[abc]	9 (13.24%)	46 (42.20%)	86 (65.65%)	141 (45.78%)
Coagulation failure[abc]	0 (0.00%)	54 (49.54%)	90 (68.70%)	144 (46.75%)
Brain failure[bc]	3 (4.41%)	12 (11.01%)	58 (44.27%)	73 (23.70%)
Circulatory failure[bc]	1 (1.47%)	6 (5.50%)	55 (41.98%)	62 (20.13%)
Respiratory failure[bc]	0 (0.00%)	3 (2.75%)	43 (32.82%)	46 (14.94%)
MELD at listing[ab]				
Median (Q1-Q3)	27.0 (20.5 - 30.0)	31.0 (26.0 - 36.0)	33.0 (21.0 - 40.0)	30.0 (23.0 - 37.0)
CLIF-C ACLF score[abc]				
Median (Q1-Q3)	44.5 (40.0 - 51.0)	51.0 (45.0 - 58.0)	63.0 (54.0 - 72.0)	53.0 (46.0 - 64.0)
Missing (%)	0 (0.00%)	5 (4.59%)	20 (15.27%)	25 (8.12%)
>64	6 (8.82%)	15 (13.76%)	44 (33.59%)	65 (21.10%)
Transplant[b]	60 (88.24%)	87 (79.82%)	87 (66.41%)	234 (75.97%)
Time (in days) from wait-listing for ACLF ** to transplant / death / delisting[abc]				
Median (Q1-Q3)	20.0 (8.0 - 37.5)	8.0 (4.0 - 18.0)	5.0 (2.0 - 11.0)	8.0 (3.0 - 19.5)
Death[bc]	18 (26.47%)	31 (28.44%)	62 (47.33%)	111 (36.04%)
Follow-up time (in months) from wait-listing for ACLF* to death / end of follow-up[b]				
Median (Q1-Q3)	11.7 (7.5 - 18.3)	10.2 (5.7 - 16.2)	7.1 (0.3 - 16.5)	9.8 (1.4 - 17.1)

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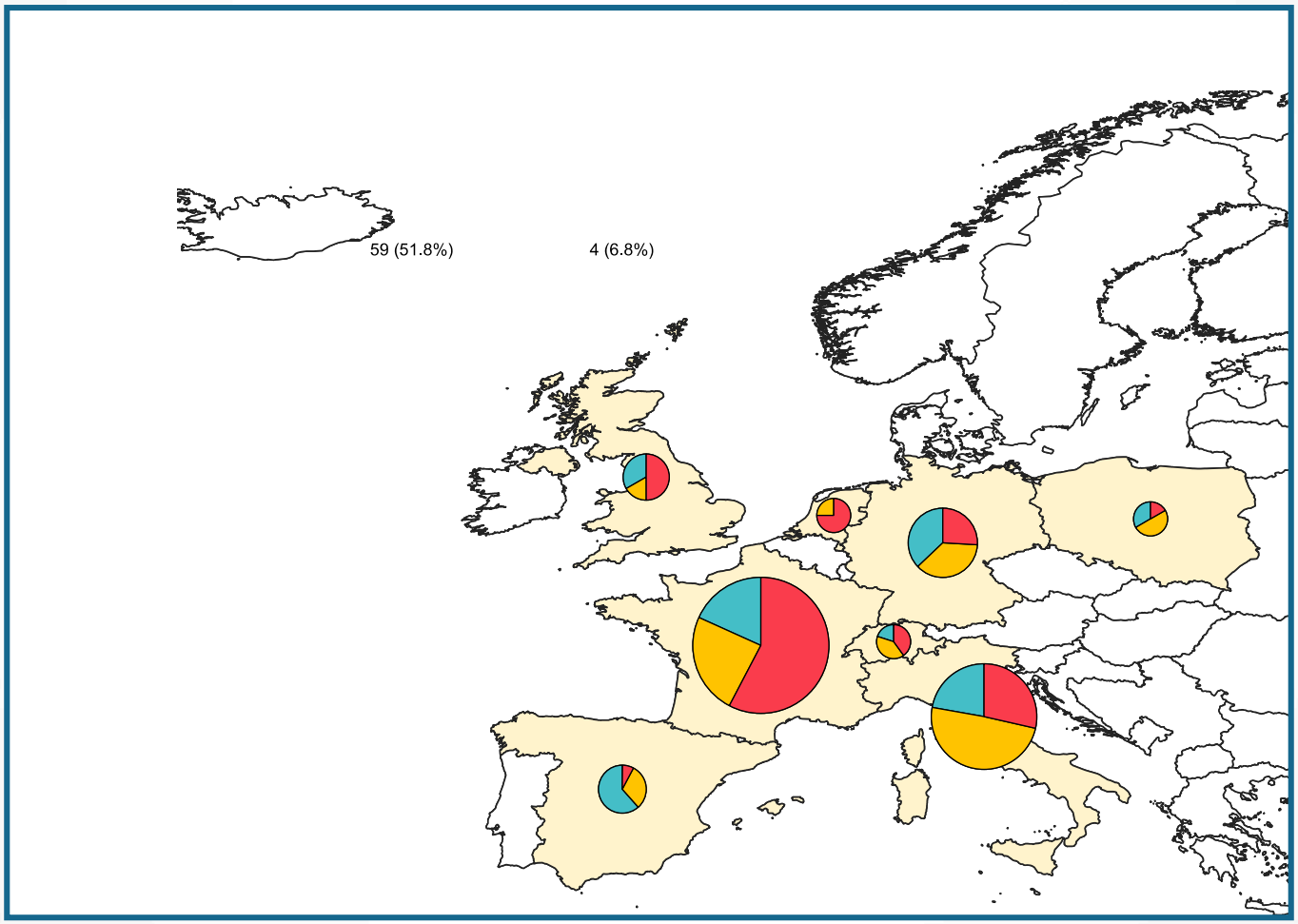
ACLF cases enrolled in the study by country



EF Clif
EUROPEAN FOUNDATION FOR THE STUDY OF CHRONIC LIVER FAILURE

ELITA
European Liver and Intestine Transplant Association

European Liver Transplant Registry

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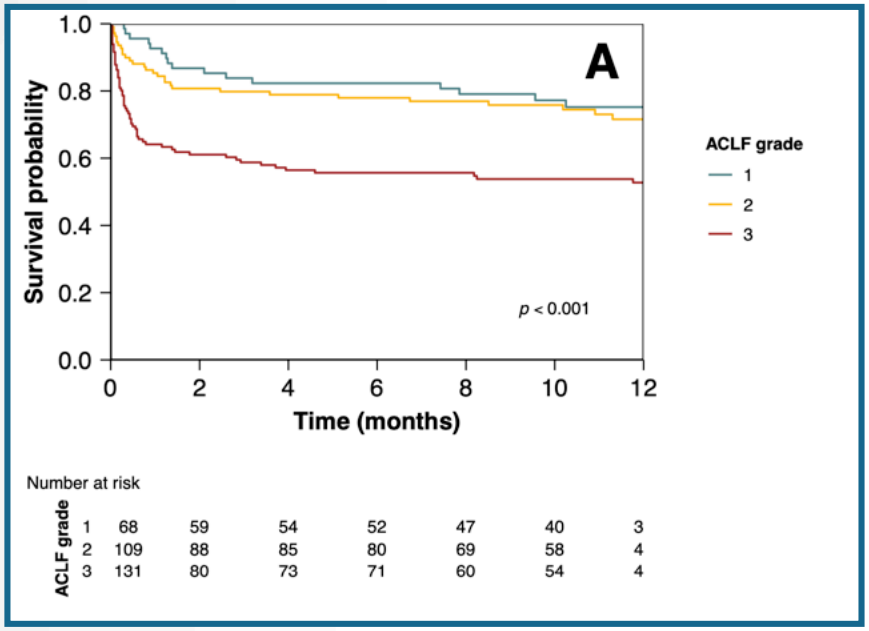
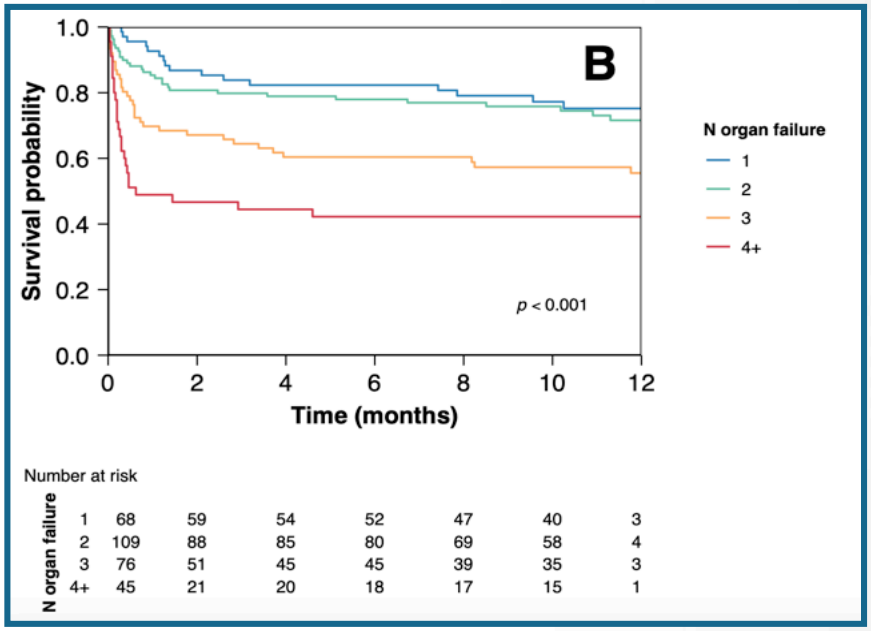
Survival curves from waitlisting for ACLF or from occurrence of ACLF if it occurred after listing





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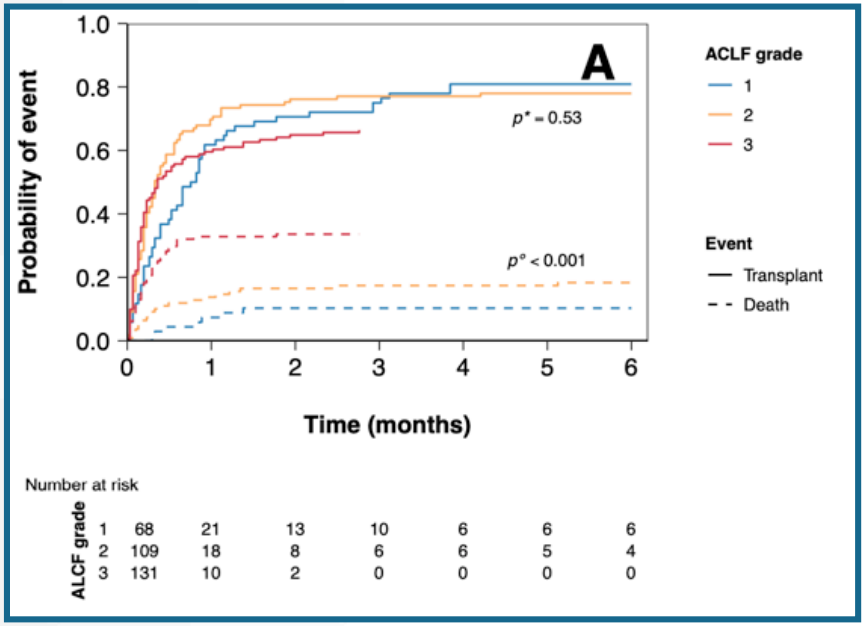
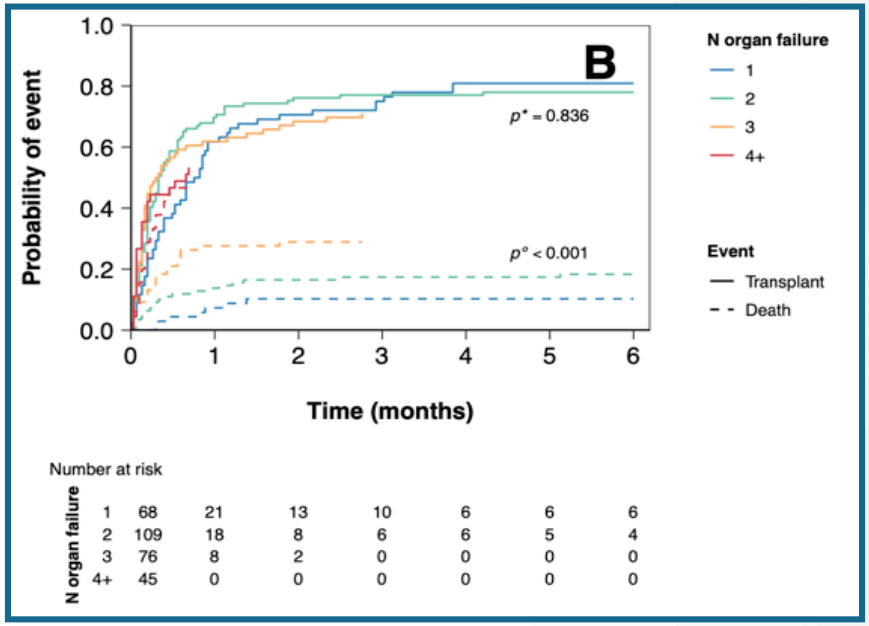
Cumulative incidence of transplant and death





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Analysis of predictors of death or delisting before LT (competing risks model).

Variable	Univariate model		Multivariate model	
	Hazard Ratio (95% Confidence Interval)	p-value	Hazard Ratio (95% Confidence Interval)	p-value
Incident case	2.77 (1.75 - 4.39)	<.0001	**1.87 (1.12 - 3.13)**	**0.0167**
ACLF baseline				
2 vs 1	1.82 (0.83 - 3.99)	0.1331		
3 vs 1	3.47 (1.68 - 7.19)	0.0008		
Sex (male vs female)	1.06 (0.66 - 1.72)	0.8043		
Age >60	2.03 (1.29 - 3.19)	0.0023	**1.89 (1.15 - 3.11)**	**0.0118**
Number of organ failure				
2 vs 1	1.82 (0.83 - 4.00)	0.1329	**1.97 (0.93 - 4.15)**	**0.0755**
3 vs 1	2.85 (1.30 - 6.26)	0.0091	**2.85 (1.33 - 6.12)**	**0.0073**
4+ vs 1	5.53 (2.49 - 12.29)	<.0001	**5.29 (2.39 - 11.70)**	**<.0001**
Organ failure				
Liver failure	0.85 (0.45 - 1.59)	0.6006		
Kidney failure	2.32 (1.45 - 3.71)	0.0004		
Coagulation failure	1.11 (0.70 - 1.76)	0.6452		
Brain failure	1.92 (1.19 - 3.09)	0.0075		
Circulatory failure	2.31 (1.40 - 3.82)	0.001		
Respiratory failure	3.59 (2.19 - 5.87)	<.0001		
MELD at listing (1-unit increase)	0.96 (0.93 - 0.99)	0.006		
CLIF-C ACLF score classes				
40-52 vs ≤ 40	0.83 (0.16 - 4.32)	0.8249		
52-64 vs ≤ 40	3.25 (0.74 - 14.23)	0.1177		
>64 vs ≤ 40	12.94 (3.09 - 54.27)	0.0005		
Type of precipitating event (multiple events possible)				
Infection	1.02 (0.62 - 1.67)	0.9378		
Alcohol	0.38 (0.14 - 1.02)	0.0545		
Bleeding	1.44 (0.87 - 2.40)	0.1552		
Other	0.27 (0.07 - 1.10)	0.0668		
MDRO infection	4.55 (2.90 - 7.16)	<.0001	**3.83 (2.27 - 6.46)**	**<.0001**
Gram positive	4.09 (2.05 - 8.18)	<.0001		
Gram negative	2.81 (1.69 - 4.66)	<.0001		
Other	5.82 (3.18 - 10.64)	<.0001		

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Characteristics of patients receiving a liver transplant

	ACLF at LT			Total (N=234)
	1 (N=58)	2 (N=78)	3 (N=98)	
PATIENTS' FEATURES				
ACLF occurring after listing[ab]	21 (36.21%)	13 (16.67%)	14 (14.29%)	48 (20.51%)
Type of organ failure				
Liver failure[ab]	32 (55.17%)	69 (88.46%)	88 (89.80%)	189 (80.77%)
Renal failure[bc]	16 (27.59%)	23 (29.49%)	64 (65.31%)	103 (44.02%)
Coagulation failure[ab]	8 (13.79%)	50 (64.10%)	76 (77.55%)	134 (57.26%)
Brain failure[bc]	2 (3.45%)	8 (10.26%)	50 (51.02%)	60 (25.64%)
Circulatory failure[bc]	0 (0.00%)	5 (6.41%)	48 (48.98%)	53 (22.65%)
Respiratory failure[bc]	0 (0.00%)	1 (1.28%)	28 (28.57%)	29 (12.39%)
PaO2/FiO2 at LT				
Median (Q1-Q3)	-	-	253.5 (195.0 - 296.0)	253.5 (195.0 - 296.0)
PaO2/FiO2 at LT <200	-	-	6 (21.43%)	6 (20.69%)
MELD at LT[abc]				
Median (Q1-Q3)	28.0 (25.0 - 32.0)	34.0 (30.0 - 38.0)	38.5 (33.0 - 40.0)	34.0 (30.0 - 39.0)
MELD at LT >30[ab]	20 (34.48%)	57 (73.08%)	84 (85.71%)	161 (68.80%)
MELD at LT >35[abc]	5 (8.62%)	30 (38.46%)	61 (62.24%)	96 (41.03%)
CLIF-C ACLF score at LT[abc]				
Median (Q1-Q3)	43.0 (39.0 - 47.0)	50.5 (46.0 - 55.0)	62.0 (55.0 - 67.0)	52.0 (45.0 - 61.0)
Classes[abc]				
≤40	22 (37.93%)	7 (8.97%)	2 (2.04%)	31 (13.25%)
40-52	32 (55.17%)	38 (48.72%)	17 (17.35%)	87 (37.18%)
52-64	4 (6.90%)	30 (38.46%)	43 (43.88%)	77 (32.91%)
>64	0 (0.00%)	3 (3.85%)	35 (35.71%)	38 (16.24%)
Pre-LT MDRO infection				
Yes	6 (10.34%)	4 (5.13%)	13 (13.27%)	23 (9.83%)
Lactate before LT (mmol/L)				
Median (Q1-Q3)	1.6 (1.4 - 2.5)	2.1 (1.6 - 2.8)	2.0 (1.5 - 2.9)	2.0 (1.4 - 2.7)
Missing (%)	16 (27.59%)	8 (10.26%)	2 (2.04%)	26 (11.11%)
Lactate >4	2 (3.45%)	4 (5.13%)	14 (14.29%)	20 (8.55%)

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Characteristics of patients receiving a liver transplant

	ACLF at LT			Total (N = 234)
	1 (N = 58)	2 (N = 78)	3 (N = 98)	
POST-LT FEATURES				
Intubation >48 hrs[bc], N of pts (%)	10 (17.24%)	18 (23.08%)	44 (44.90%)	72 (30.77%)
Days of intubation				
Median (Q1-Q3)	7.0 (3.0 - 15.0)	6.0 (4.0 - 12.0)	9.5 (4.0 - 23.0)	8.0 (4.0 - 20.0)
RRT[bc], N of pts (%)	15 (25.86%)	18 (23.08%)	46 (46.94%)	79 (33.76%)
Days of RRT				
Median (Q1-Q3)	8.0 (3.0 - 22.0)	13.0 (6.0 - 19.0)	11.0 (4.0 - 24.0)	11.0 (4.0 - 22.0)
Length (days) of total hospital stay after LT[b]				
Median (Q1-Q3)	24.0 (18.0 - 39.0)	30.0 (21.0 - 54.0)	37.5 (24.5 - 69.5)	32.0 (21.0 - 55.0)
Length (days) of ICU stay after LT[b]				
Median (Q1-Q3)	7.5 (5.0 - 13.0)	10.0 (6.0 - 17.0)	12.5 (7.0 - 29.0)	11.0 (6.0 - 20.0)
Post-LT MDRO infections				
Yes	14 (24.14%)	15 (19.23%)	30 (30.61%)	59 (25.21%)
Death	6 (10.34%)	12 (15.38%)	19 (19.39%)	37 (15.81%)
Follow-up time (in days) from wait-listing for ACLF* to transplant[ab]				
Median (Q1-Q3)	17.0 (8.0 - 32.0)	6.5 (3.0 - 17.0)	6.0 (2.0 - 13.0)	7.0 (3.0 - 20.0)
Follow-up time (in months) from transplant to death / end of follow-up				
Median (Q1-Q3)	13.1 (7.4 - 17.4)	10.7 (7.4 - 16.7)	12.7 (7.6 - 17.9)	12.0 (7.5 - 17.6)
Follow-up time (in months) from wait-listing for ACLF* to death / end of follow-up				
Median (Q1-Q3)	15.5 (8.2 - 18.7)	11.8 (8.0 - 17.7)	13.0 (7.7 - 18.2)	13.0 (8.0 - 18.4)

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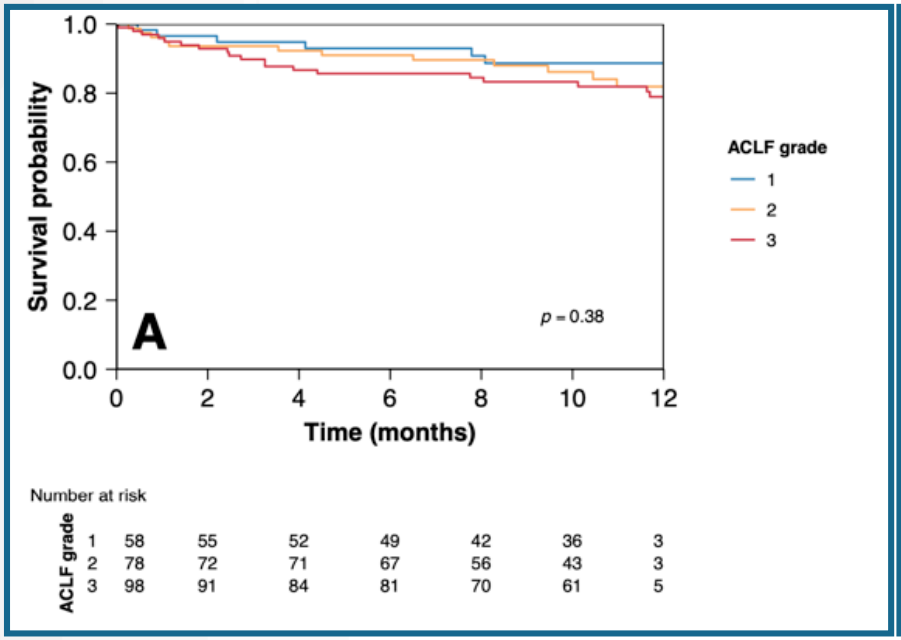
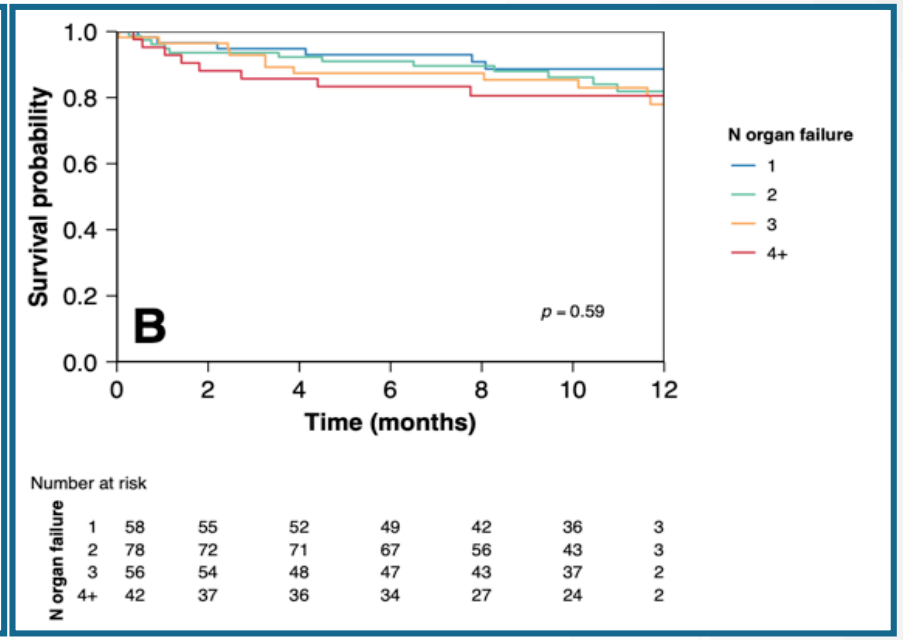
Survival curves from liver transplant





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Analysis of predictors of death after transplant

Variable	Univariate models		Multivariate model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Incident case	1.81 (0.89 - 3.66)	0.1		
ACLF at LT				
2 vs 1	1.51 (0.57 - 4.03)	0.4071		
3 vs 1	1.89 (0.75 - 4.73)	0.1743		
Sex (male vs female)	1.02 (0.51 - 2.03)	0.9545		
Age >60	0.54 (0.23 - 1.30)	0.1717		
Number of organ failure				
2 vs 1	1.51 (0.57 - 4.03)	0.4071		
3 vs 1	1.87 (0.69 - 5.05)	0.2193		
4+ vs 1	1.92 (0.67 - 5.54)	0.2261		
Organ failure				
Liver	1.01 (0.44 - 2.29)	0.9879		
Kidney	1.99 (1.03 - 3.83)	0.0401		
Coagulation	0.96 (0.50 - 1.85)	0.9114		
Brain	1.87 (0.96 - 3.64)	0.0643		
Circulatory	1.30 (0.63 - 2.69)	0.4746		
Respiratory	0.59 (0.18 - 1.93)	0.387		
PaO2/FiO2 at LT <200	0.95 (0.13 - 6.90)	0.9562		
Severe alcoholic hepatitis	0.59 (0.18 - 1.93)	0.3833		
MELD at LT (1 unit increase)	1.05 (1.00 - 1.11)	0.0436		
MELD >30	1.66 (0.76 - 3.63)	0.2047		
MELD >35	1.73 (0.91 - 3.31)	0.096		
CLIF-C ACLF score at LT (classes)				
40-52 vs <= 40	3.06 (0.71 - 13.32)	0.1353		
52-64 vs <= 40	2.39 (0.53 - 10.80)	0.2561		
>64 vs <= 40	3.67 (0.78 - 17.27)	0.1002		

Variable	Univariate models		Multivariate model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Type of precipitating event (multiple events possible)				
Infection	1.28 (0.61 - 2.68)	0.5192		
Alcohol	0.17 (0.02 - 1.21)	0.0764		
Bleeding	1.36 (0.63 - 2.92)	0.4328		
Other	1.51 (0.58 - 3.91)	0.3974		
Pre-LT MDRO infection	**3.86 (1.82 - 8.21)**	**0.0004**	**3.67 (1.63 - 8.28)**	**0.0017**
Gram positive	2.33 (0.32 - 16.99)	0.4051		
Gram negative	2.89 (1.20 - 6.95)	0.0178		
Other	26.25 (5.71 - 120.63)	<.0001		
Lactate before LT (1-unit increase)	1.07 (0.96 - 1.20)	0.1944		
Lactate at LT >4 mmol/L	**3.63 (1.64 - 8.04)**	**0.0015**	**3.14 (1.37 - 7.19)**	**0.0069**
WBC before LT (1-unit increase)	1.01 (0.97 - 1.06)	0.6503		
Intubation >48 hrs	4.11 (2.11 - 7.99)	<.0001		
RRT	**2.86 (1.49 - 5.48)**	**0.0016**	**2.74 (1.37 - 5.51)**	**0.0046**
Donor age (1-unit increase)	1.02 (0.99 - 1.04)	0.1668		
WIT in min (1-minute increase)	1.00 (0.99 - 1.01)	0.4667		
CIT in min (1-minute increase)	1.00 (1.00 - 1.00)	0.7306		
Time from listing to LT (1-day increase)	1.00 (0.99 - 1.01)	0.8561		

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Table S1. Description of MDRO infections.

	ACLF at listing or at occurrence (if after listing)			Total (N=308)
	ACLF-1 (N=68)	ACLF-2 (N=109)	ACLF-3 (N=131)	
MDRO infection – N (%)				
Yes	10 (14.71%)	14 (12.84%)	31 (23.66%)	55 (17.86%)
Missing	*0 (0.00%)*	*1 (0.92%)*	*0 (0.00%)*	*1 (0.32%)*
Organisms (multiple organisms possible) – N (%*)				
Gram positive	1 (10.00%)	1 (7.14%)	4 (12.90%)	6 (10.91%)
VRE	*1 (10.00%)*	*0 (0.00%)*	*2 (6.45%)*	*3 (5.45%)*
MRSA/VRSA	*0 (0.00%)*	*1 (7.14%)*	*2 (6.45%)*	*3 (5.45%)*
Gram negative	7 (70.00%)	11 (78.57%)	22 (70.97%)	40 (72.73%)
Carbapenem resistant	*1 (10.00%)*	*0 (0.00%)*	*3 (9.68%)*	*4 (7.27%)*
ESBL	*6 (60.00%)*	*10 (71.43%)*	*18 (58.06%)*	*34 (61.82%)*
Amp-c Enterobacter or Amp-c Citrobacter	*0 (0.00%)*	*1 (7.14%)*	*1 (3.23%)*	*2 (3.64%)*
Other	2 (20.00%)	2 (14.29%)	7 (22.58%)	11 (20.00%)
Fungi	*1 (10.00%)*	*1 (7.14%)*	*4 (12.90%)*	*6 (10.91%)*
Other	*1 (10.00%)*	*1 (7.14%)*	*3 (9.68%)*	*5 (9.09%)*
Site (multiple sites possible) - N (%*)				
Spontaneous or secondary bacteremia	2 (20.00%)	7 (50.00%)	12 (38.71%)	21 (38.18%)
Spontaneous bacterial peritonitis	1 (10.00%)	4 (28.57%)	4 (12.90%)	9 (16.36%)
Pneumonia	3 (30.00%)	2 (14.29%)	9 (29.03%)	14 (25.45%)
Urinary tract infection	3 (30.00%)	1 (7.14%)	7 (22.58%)	11 (20.00%)
Skin or soft tissue	1 (10.00%)	1 (7.14%)	2 (6.45%)	4 (7.27%)
Cholangitis or liver abscesses	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.82%)

The distributions of all variables were compared among ACLF classes using Chi-square or Fisher's exact test. Bonferroni's method was used to account for multiple comparisons. No pairwise comparison was statistically significant at a 0.05 level.
** Refers to patients experiencing an infection (first row)*

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Table S3. Description of MDRO infections of patients who died in the waiting list.

	ACLF at listing or at occurrence (if after listing)			Total (N=74)
	1 (N=8)	2 (N=22)	3 (N=44)	
MDRO infection – N (%)	5 (62.50%)	10 (47.62%)	13 (36.11%)	28 (43.08%)
Organism (multiple organisms possible) – N (%*)				
Gram positive	1 (20.00%)	1 (10.00%)	2 (15.38%)	4 (14.29%)
VRE	1 (20.00%)	0 (0.00%)	1 (7.69%)	2 (7.14%)
MRSA/VRSA	0 (0.00%)	1 (10.00%)	1 (7.69%)	2 (7.14%)
Gram negative	2 (40.00%)	8 (80.00%)	8 (61.54%)	18 (64.29%)
Carbapenem resistant	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)
ESBL	1 (20.00%)	8 (80.00%)	8 (61.54%)	17 (60.71%)
Other	2 (40.00%)	1 (10.00%)	5 (38.46%)	8 (28.57%)
Fungi	1 (20.00%)	0 (0.00%)	3 (23.08%)	4 (14.29%)
Other	1 (20.00%)	1 (10.00%)	2 (15.38%)	4 (14.29%)
Site (multiple sites possible) – N (%*)				
Spontaneous or secondary bacteremia	2 (40.00%)	6 (60.00%)	5 (38.46%)	13 (46.43%)
Spontaneous bacterial peritonitis	0 (0.00%)	3 (30.00%)	0 (0.00%)	3 (10.71%)
Pneumonia	3 (60.00%)	1 (10.00%)	6 (46.15%)	10 (35.71%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	3 (23.08%)	3 (10.71%)
Skin and soft tissue infection	1 (20.00%)	1 (10.00%)	0 (0.00%)	2 (7.14%)

The distributions of all variables were compared among ACLF classes using Chi-square or Fisher's exact test. Bonferroni's method was used to account for multiple comparisons. No pairwise comparison was statistically significant at a 0.05 level.
** Refers to patients experiencing an infection (first row)*

- 74 patients with ACLF **died** after listing, with **infection** being **the most frequent precipitant** (63.5% [47/74]).
- **Infections from MDROs** were observed in **60%** of patients who **died** (28/47) with mortality being directly related to MDROs in 26 patients.

Table S5. Description of MDRO infections of transplanted patients.

	ACLF at LT			Total (N=234)
	1 (N=58)	2 (N=78)	3(N=98)	
Pre-LT MDRO infection – N (%)	6 (10.34%)	4 (5.13%)	13 (13.27%)	23 (9.83%)
Organism (multiple organism possible) – N (%*)				
Gram positive	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.35%)
VRE	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.35%)
Gram negative	5 (83.33%)	3 (75.00%)	12 (92.31%)	20 (86.96%)
Carbapenem resistant	0 (0.00%)	0 (0.00%)	2 (15.38%)	2 (8.70%)
ESBL	4 (66.67%)	3 (75.00%)	9 (69.23%)	16 (69.57%)
Amp-c Enterobacter or Amp-c Citrobacter	1 (16.67%)	0 (0.00%)	1 (7.69%)	2 (8.70%)
Other	0 (0.00%)	1 (25.00%)	1 (7.69%)	2 (8.70%)
Fungi	0 (0.00%)	1 (25.00%)	1 (7.69%)	2 (8.70%)
Post-LT MDRO infection – N (%)	14 (24.14%)	15 (19.23%)	30 (30.61%)	59 (25.21%)
Germ (multiple germs possible) – N (%°)				
Gram positive	3 (21.43%)	2 (13.33%)	1 (3.33%)	6 (10.17%)
VRE	3 (21.43%)	1 (6.67%)	0 (0.00%)	4 (6.78%)
MRSA/VRSA	0 (0.00%)	1 (6.67%)	0 (0.00%)	1 (1.69%)
Gram negative	11 (78.57%)	10 (66.67%)	28 (93.33%)	49 (83.05%)
Carbapenem resistant	1 (7.14%)	2 (13.33%)	8 (26.67%)	11 (18.64%)
ESBL	6 (42.86%)	8 (53.33%)	15 (50.00%)	29 (49.15%)
Amp-c Enterobacter or Amp-c Citrobacter	4 (28.57%)	0 (0.00%)	7 (23.33%)	11 (18.64%)
Other	1 (7.14%)	3 (20.00%)	3 (10.00%)	7 (11.86%)
Fungi	1 (7.14%)	3 (20.00%)	2 (6.67%)	6 (10.17%)
Other	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.69%)

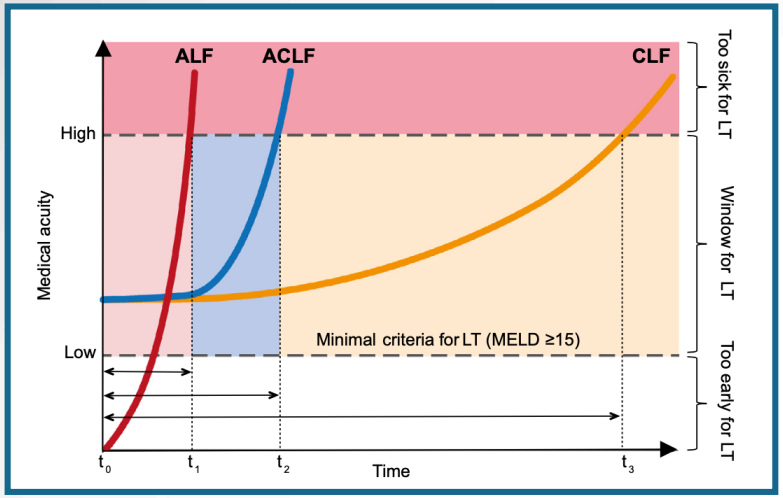
Table S6. Description of pre-LT infections and post-LT re-infections for MDRO and deaths, among patients who experienced a pre-LT MDRO infection. In the columns are reported the pre-LT MDRO infection and in rows the post-LT MDRO infections, the intersection between columns and rows describes how many patients have that specific combination of pre- and post-LT infections and how many of them died post-LT.

	Pre-LT MDRO infection											
	Gram-positive		Gram-negative									
	VRE (N=1)		*Carbapenem resistant (N=2)*		*ESBL(N=16)*		*Amp-c Enterobacter or Amp-c Citrobacter (N=2)*		Fungi (N=2)		Total (N=23)	
Post-LT MDRO infection	**N**	**Deaths (%)**	**N**	**Deaths (%)**	**N**	**Deaths (%)**	**N**	**Deaths (%)**	**N**	**Deaths (%)**	**N**	**Deaths (%)**
Gram-positive												
VRE (N=1)	1	0 (0.0%)									1	0 (0.0%)
Gram-negative												
Carbapenem resistant (N=2)			2	1 (50.0%)							2	1 (50.0%)
ESBL (N=8)					7	3 (42.9%)	1	1 (100.0%)			8	4 (50.0%)
Amp-c Enterobacter or Amp-c Citrobacter (N=1)					1	1 (100.0%)					1	1 (100.0%)
Fungi (N=1)									1	1 (100.0%)	1	1 (100.0%)
Total with post-LT MDRO infection (N=13)	**1**	**0 (0.0%)**	**2**	**1 (50.0%)**	**8**	**4 (50.0%)**	**1**	**1 (100.0%)**	**1**	**1 (100.0%)**	**13**	**7 (53.9%)**
None post-LT MDRO (N=10)	-	-	-	-	8	1 (12.5%)	1	0 (0.0%)	1	1 (100.0%)	10	2 (20.0%)
Total (N=23)	**1**	**0 (0.0%)**	**2**	**1 (50.0%)**	**16**	**5 (31.3%)**	**2**	**1 (50.0%)**	**2**	**2 (100.0%)**	**23**	**9 (39.1%)**

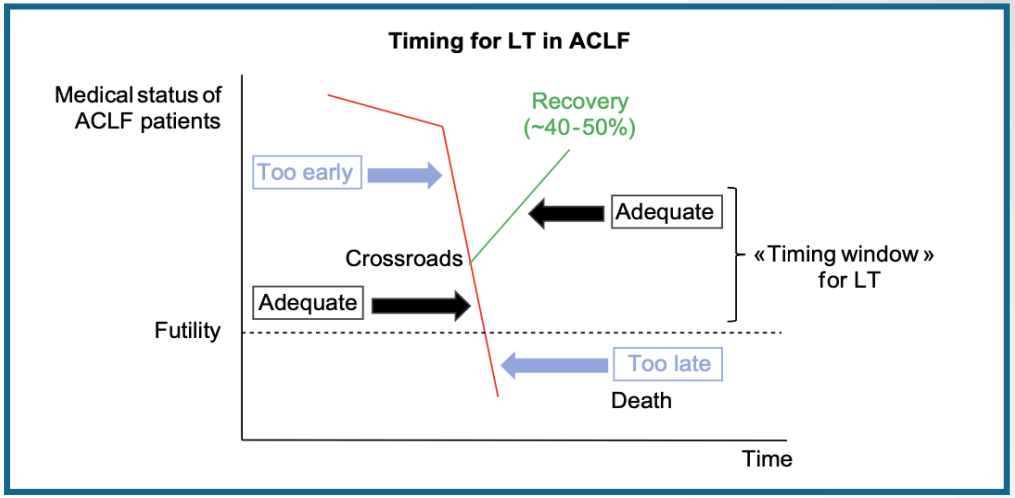
- 37/234 patients who received a LT (15.8%) died after LT.
- Main cause of death was sepsis with MOF in 21 patients.

Belli LS et al, Journal of Hepatology 2021

- Of the 23 patients with a MDRO infection pre-LT, 13 (56.5%) had a new infection from MDRO post-LT.
- In 11 cases the post-LT MDRO infection was from the same organism isolated before LT.
- 7/13 died.



Linecker M et al, Journal of Hepatology 2018



Gustot T et al, Journal of Hepatology 2018

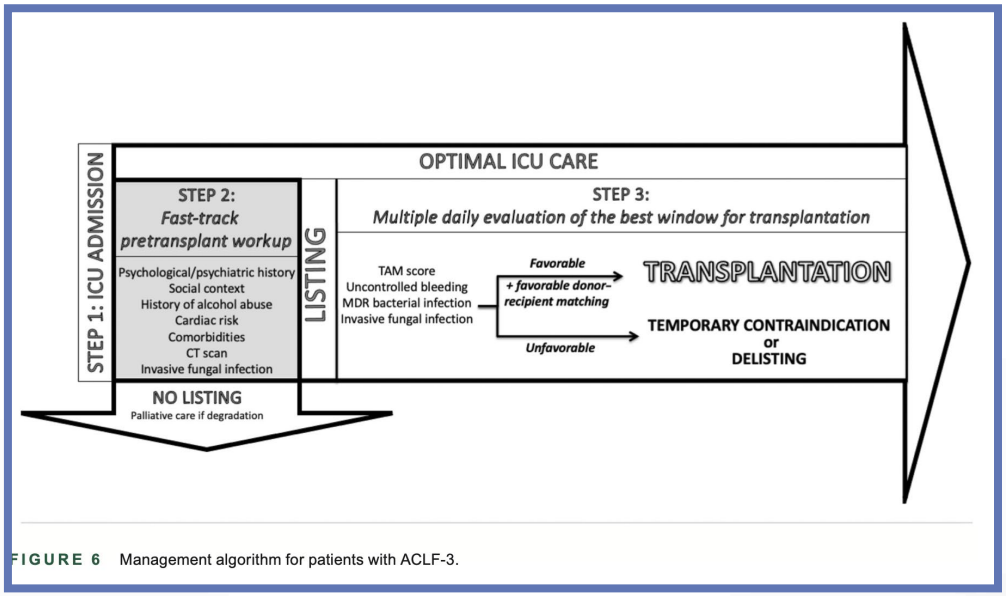
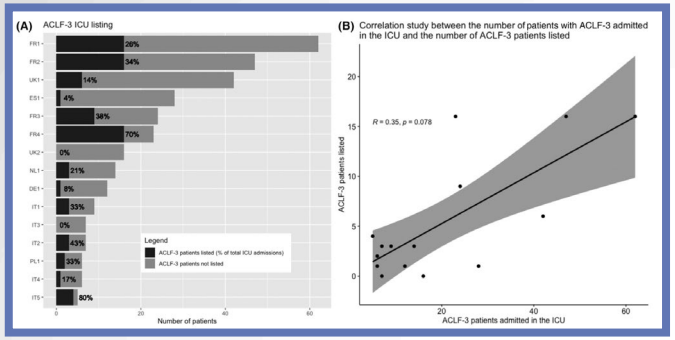


FIGURE 6 Management algorithm for patients with ACLF-3.

Artzner T et al, Liver Transplantation 2022



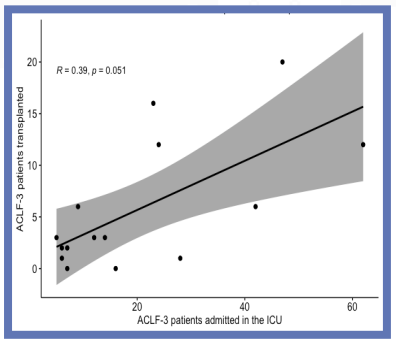
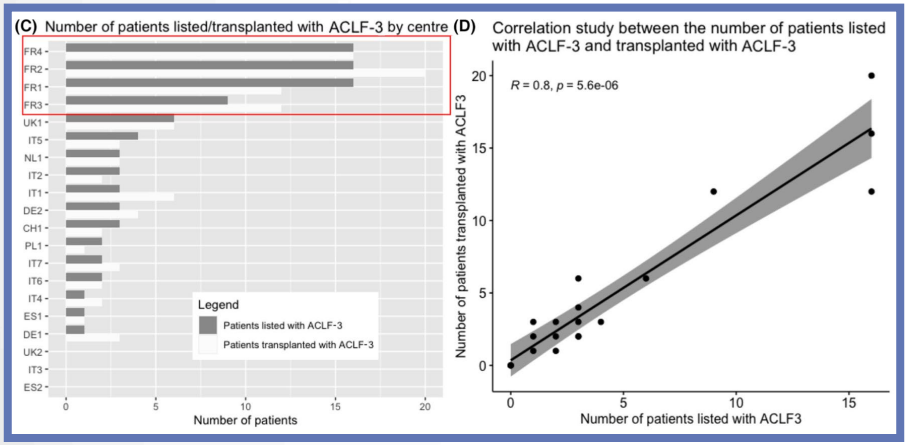


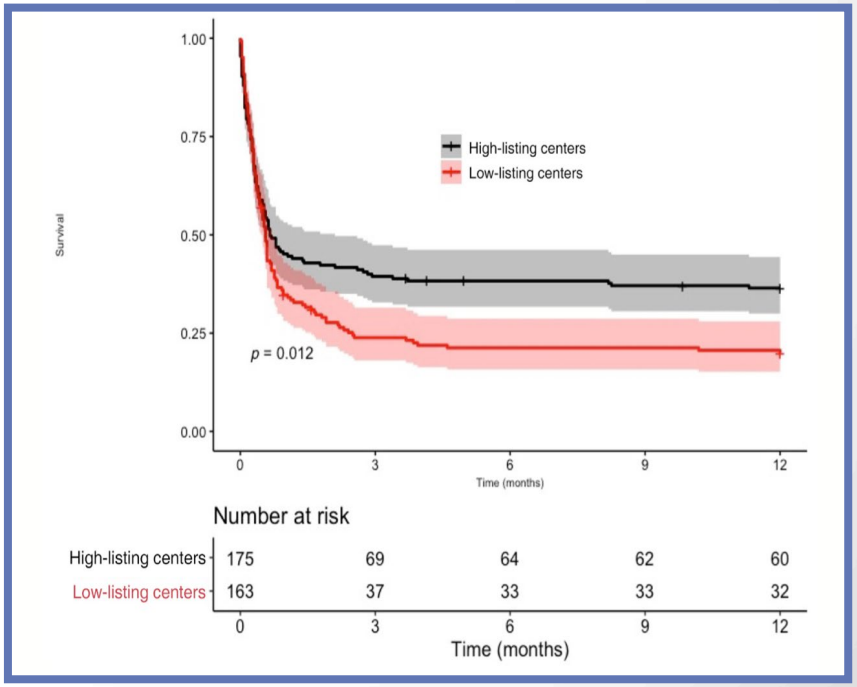
TABLE 2 Main reason for not listing patients with ACLF-3 in the ICU

Main reason for not listing	Total[a] (*N* = 227)	High-listing/transplanting centers[b] (*N* = 99)	Low-listing/transplanting centers[c] (*N* = 128)	*p* value
Illness severity	88 (39)	31 (31)	57 (46)	0.04
Addiction	62 (28)	32 (32)	30 (24)	0.14
Comorbidities	30 (13)	16 (16)	14 (11)	0.25
Uncontrolled bacterial infection	21 (9)	8 (8)	13 (10)	0.59
Other	23 (10)	12 (12)	11 (8.8)	0.38

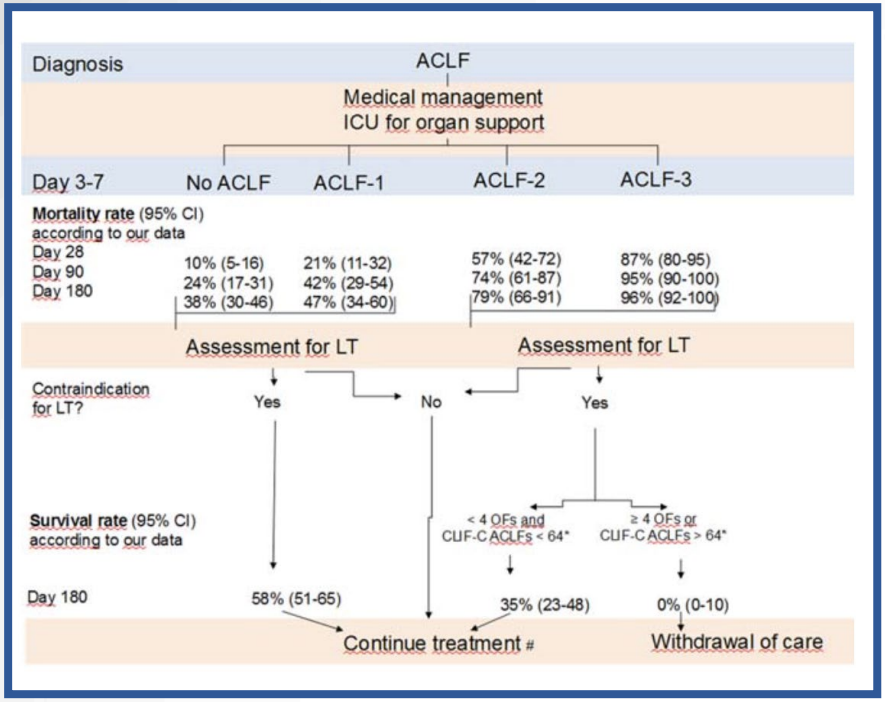
- No correlation between the number of patients admitted to the ICU and the number of patients listed with ACLF-3 or those transplanted with ACLF-3



- Significant correlation between listing and transplanting patients with ACLF-3 (correlation coefficient: 0.8; $p < 0.0001$).
- In particular, the 4 centers that transplanted the highest number of patients with ACLF-3 were also the centers that listed the highest number of patients with ACLF-3



Artzner T et al, Liver Transplantation 2022



Gustot T et al, Hepatology 2015

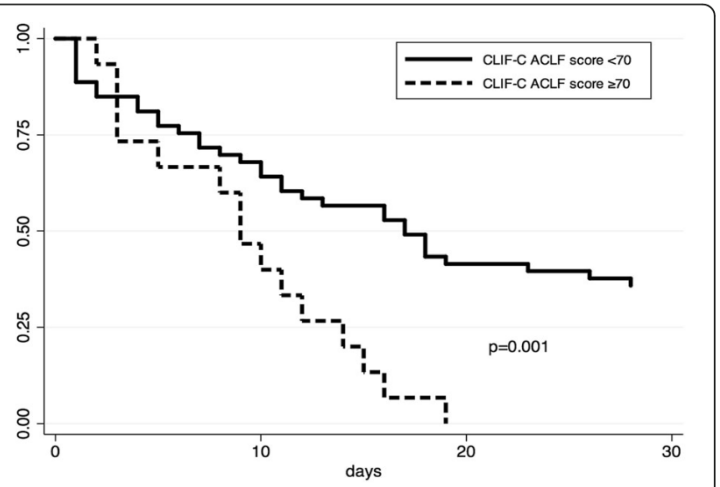


Fig. 3 Twenty-eight-day survival according to the European Foundation for the study of chronic liver failure (CLIF-C) Acute-on-Chronic Liver Failure (ACLF) score in ACLF grade 3. Low 28-day survival is noted in patients with CLIF-C ACLF score ≥ 70, 2 days after receiving full intensive treatment unit supportive therapy

CLIF-C ACLF score	28-Day mortality	Sensitivity	Specificity
≥ 55	80% (95% CI 72–85)	88% (95% CI 75–95)	42% (95% CI 20–67)
≥ 60	88% (95% CI 78–94)	78% (95% CI 63–88)	74% (95% CI 49–91)
≥ 65	94% (95% CI 79–98)	59% (95% CI 44–73)	89% (95% CI 67–99)
≥ 70	100% (95% CI 78–100)	31% (95% CI 18–45)	100% (95% CI 82–100)

Abbreviations: ACLF Acute-on-Chronic Liver Failure, *CLIF* European Foundation for the study of chronic liver failure

Engelmann et al, Critical Care 2018

Absolute contraindications for LT

- active gastrointestinal bleeding
- control of sepsis for less than 24 h
- hemodynamic instability requiring a dose of norepinephrine $\geq$ 3 mg/h
- severe lung impairment, defined by a ratio PaO2/FiO2 <150

Artru et al, J. Hepatol. 2017; 67 : 798-715

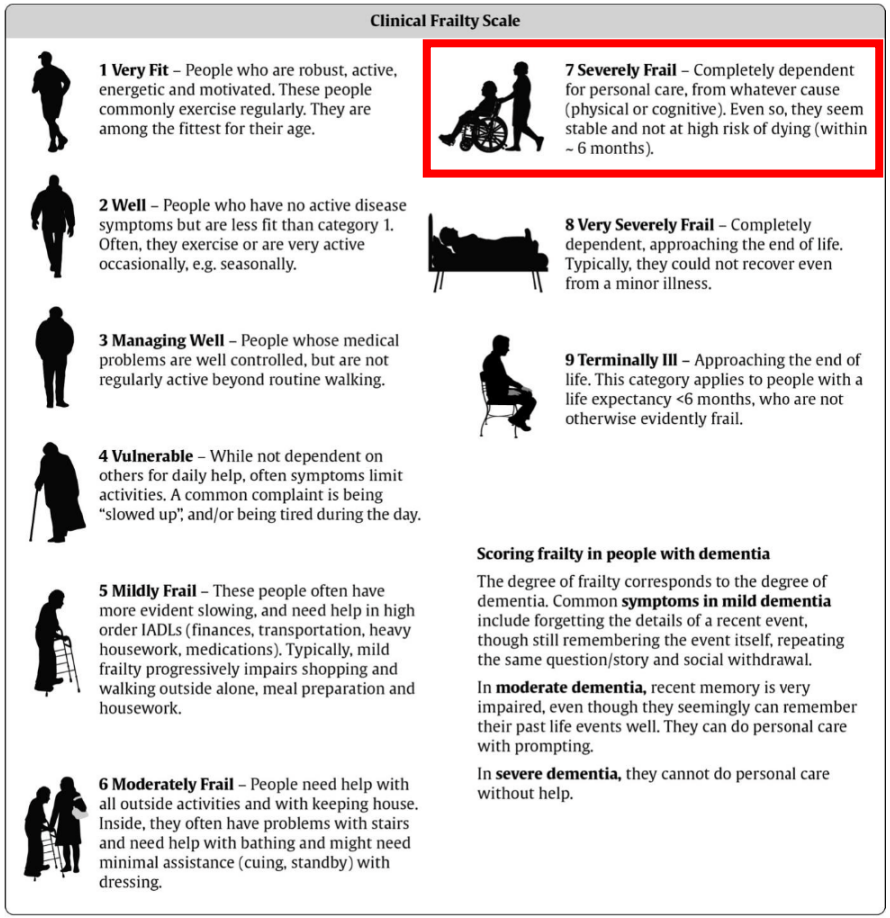
Table 5. Proposed absolute and relative pre-transplant conditions when potentially inappropriate LT has to be considered.

Absolute	Relative
Multiorgan failure with 4 or more organ systems failing (liver, kidney, lungs, circulation, brain)	Increased ventilation support (FiO_2 ≥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 waisting and malnutrition
Pulmonary hypertension with: - mPAP >50 mmHg, - mPAP 35–50 mmHg with elevated PVR - >250 dyn/s/cm^5, or - high PVR >400 dyn/s/cm^5	Aggregated severe chronic comorbidities
Severe respiratory failure requiring maximal ventilation support (FiO_2 ≥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	

mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; LT, liver transplantation; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; PEEP, positive end expiratory pressure.

Linecker M et al, Journal of Hepatology 2018

When Is a Critically Ill Cirrhotic Patient Too Sick to Transplant? Development of Consensus Criteria by a Multidisciplinary Panel of 35 International Experts



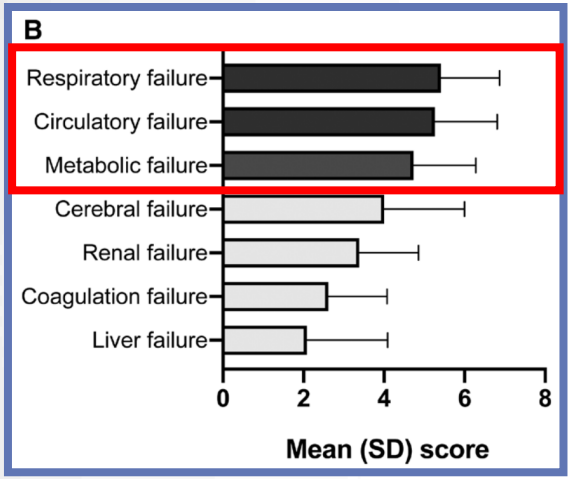
- The Delphi panelists **recommended denying LT** in case of **severe frailty**.
- No consensus was reached regarding the age of the recipient.

TABLE 1.

Consensus situations in which an infection could lead to postponing LT

Criteria (at the time of graft proposal)	Similar response rate
Persistent fever >39°C	89%
Leukopenia <500/mm^3	74%
Pneumonia treated with <72 h of appropriate antimicrobial treatment	88%
Spontaneous bacterial peritonitis treated with <72 h of appropriate antimicrobial treatment	71%
Previous infection due to a pandrug-resistant *Enterobacteriaceae*	72%

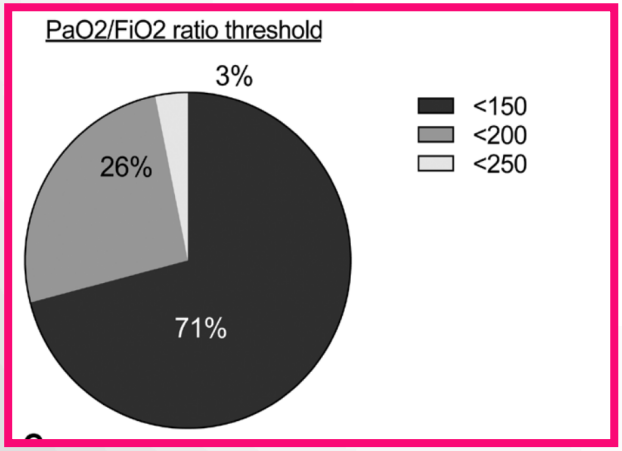
When Is a Critically Ill Cirrhotic Patient Too Sick to Transplant? Development of Consensus Criteria by a Multidisciplinary Panel of 35 International Experts

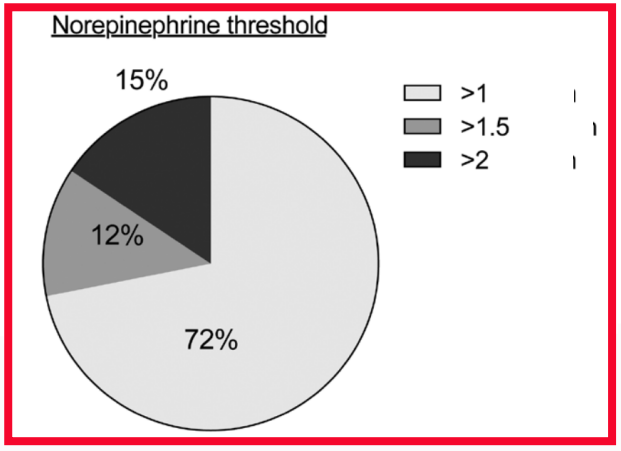


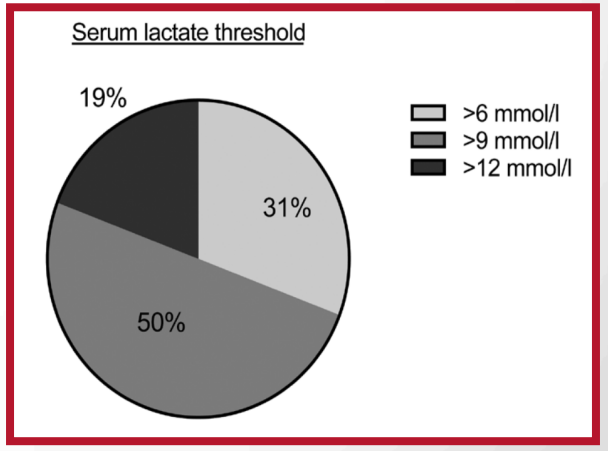
A consensus was reached ranking **respiratory**, **circulatory**, and **metabolic failures** as **essential considerations** in determining LT candidacy.

A threshold of:
- **Pao2/FiO2 ≤150** mmHg
- **norepinephrine dose ≥1** µg/kg per minute
- **lactate level ≥9** mmol/L

was considered a **contraindication** to LT.







	Points
Arterial lactate level (mmol/l)	
<4	0
≥4	1
Mechanical ventilation with PaO_2/FiO_2 ratio ≤ 200 mm Hg	
No	0
Yes	1
Age (years)	
<53	0
≥53	1
Leukocyte counts (G/l)	
>10	0
≤10	1
TAM score	= Σ

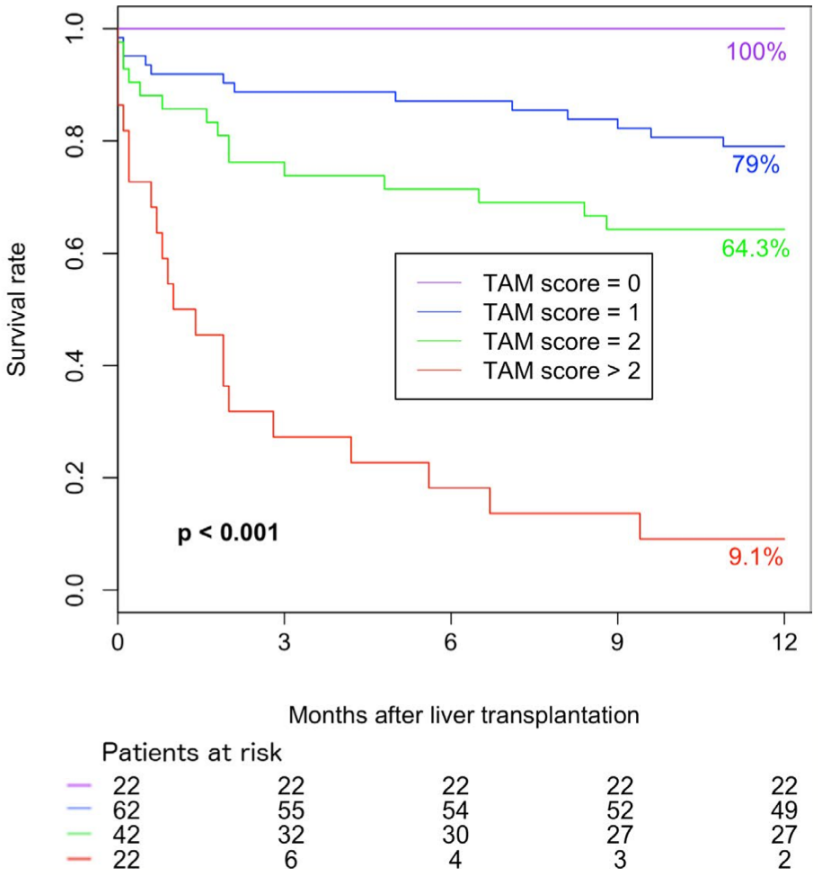


FIGURE 4 Survival rate after liver transplantation in the entire cohort (n = 148) depending on the transplantation for ACLF-3 model (TAM) score [Color figure can be viewed at wileyonlinelibrary.com]

Artzner T et al, AJT 2020

Organ allocation in the MELD era

- MELD underestimates the risk of death of ACLF patients
- Mortality of patients with ACLF in comparison to those with ALF

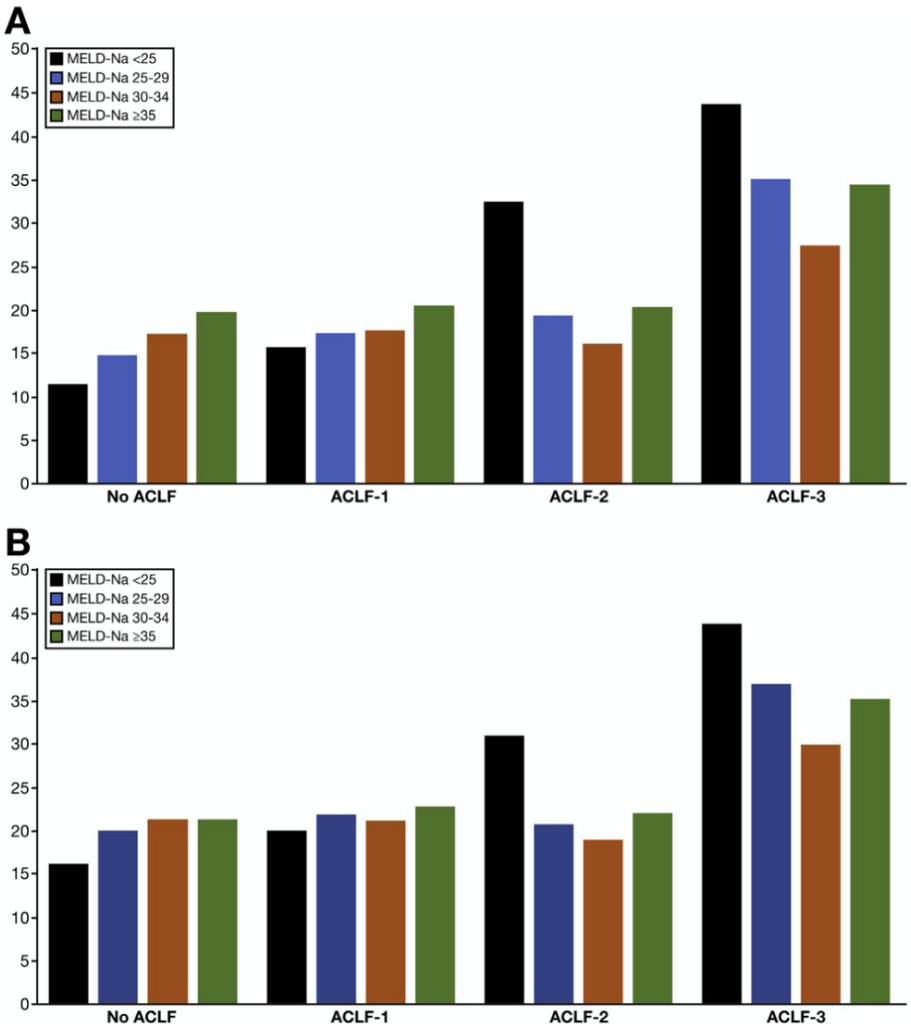
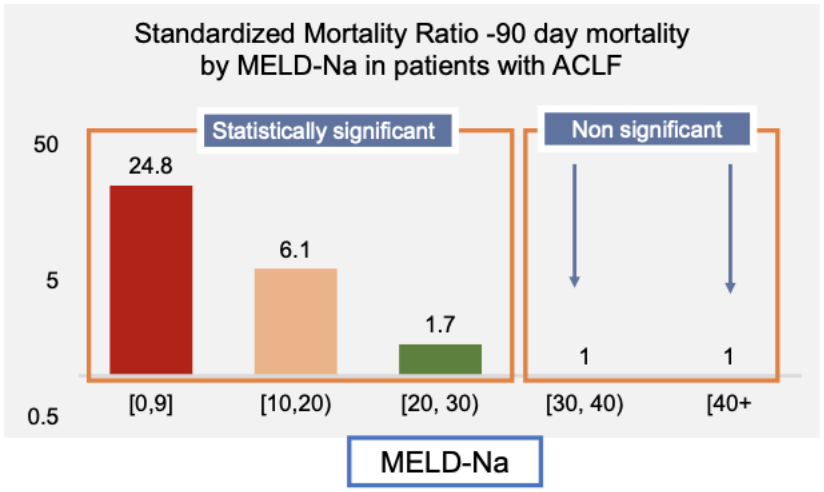
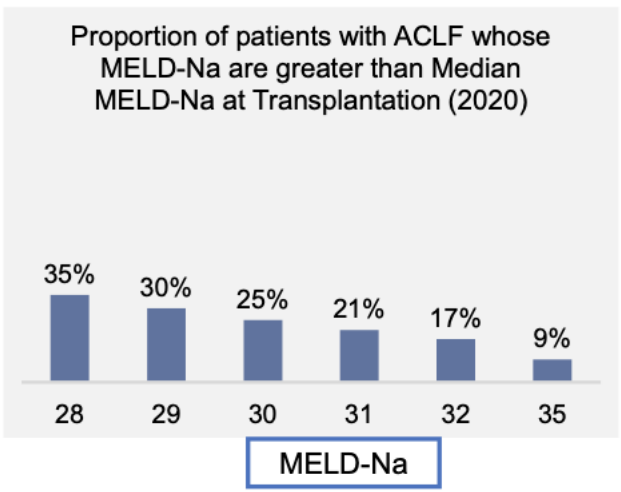


Figure 2. (*A*) Death or removal from the waiting list within 28 days, according to ACLF and MELD-Na category. (*B*) Death or removal from the waiting list within 90 days, according to ACLF and MELD-Na category.

Sundaram et al, Gastroenterology 2019

LOW MELD-NA DOES NOT PREDICT 90-DAY MORTALITY IN ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) IN AN AMERICAN COHORT



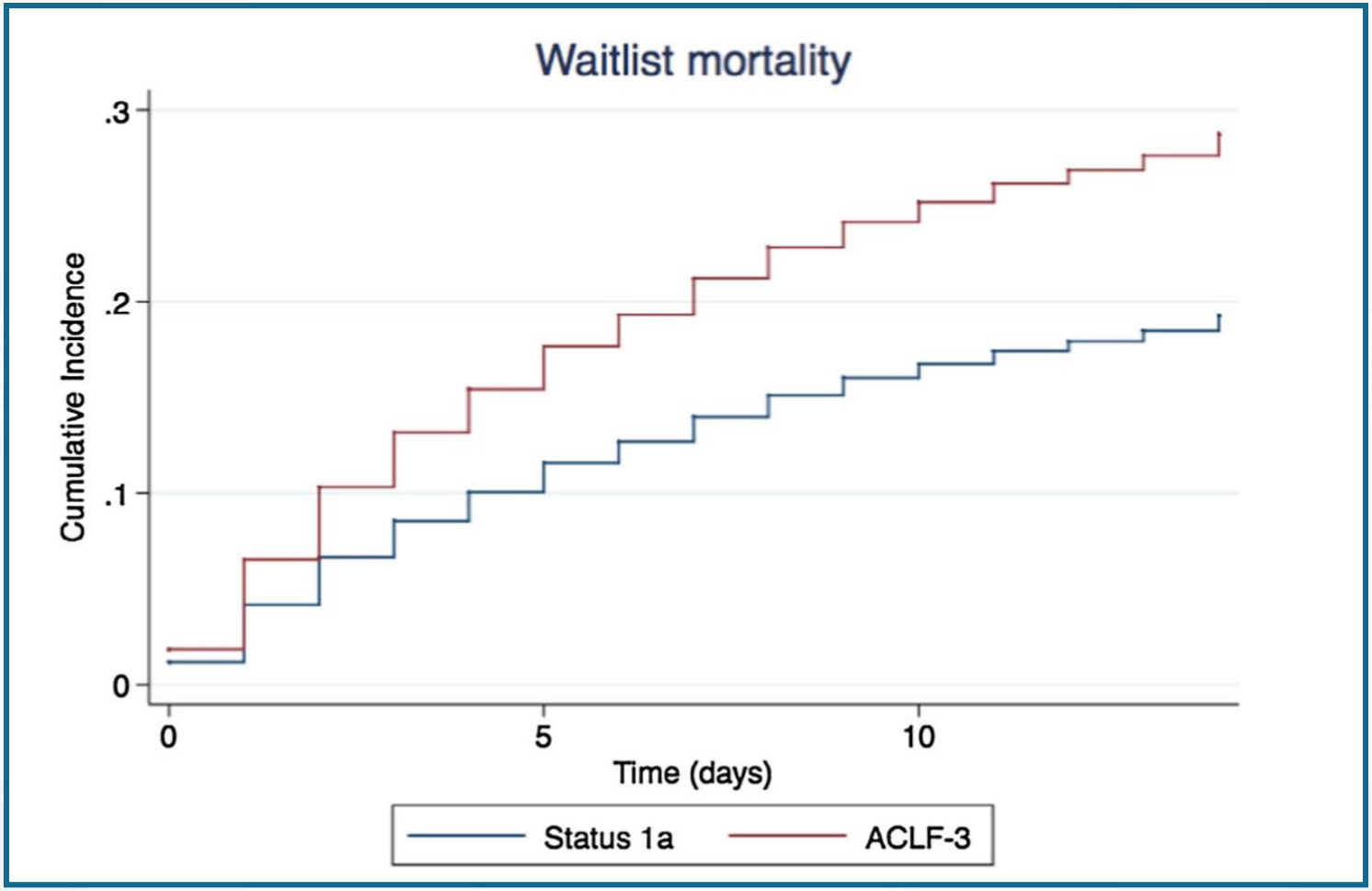


- ✓ In a multiethnic cohort of 18,979 patients with ACLF, median MELD-Na was 26 and 90 day mortality was 40%
- ✓ The observed 90-day mortality was much higher than that predicted based on MELD-Na in patients with MELD-Na ≤30
- ✓ Few ACLF patients had MELD-Na scores that exceeded the U.S. national median MELD-Na of 35.
- ✓ Providers should start liver transplant referral and evaluation independent of MELD-Na

Hernaez R et al, Journal of Hepatology 2020

Organ allocation in the MELD era

- MELD underestimates the risk of death of ACLF patients
- Mortality of patients with ACLF in comparison to those with ALF

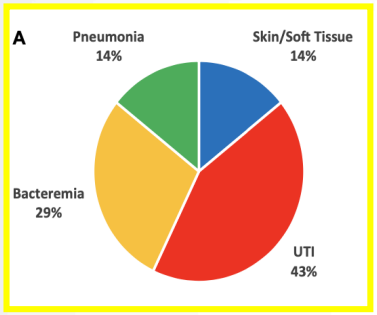


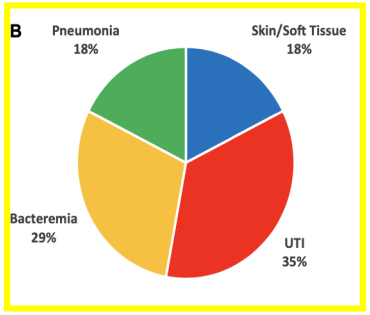
Sundaram V et al, Hepatology 2019

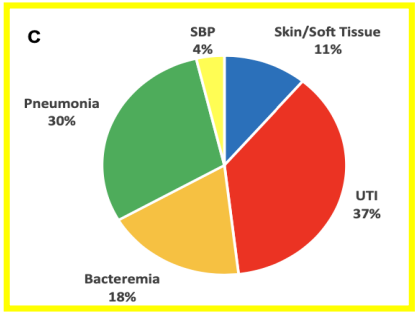
Table 2. Post-Transplant Complications Within 1 Year of Transplantation, Categorized According to Severity of ACLF at Transplant

	No ACLF (n = 106)	ACLF-1 (n = 61)	ACLF-2 (n = 74)	ACLF-3 (n = 77)	*P* value
Acute cellular rejection	2 (1.9)	6 (9.8)	4 (5.4)	10 (12.9)	.022
Biliary complications	5 (4.7)	4 (6.6)	3 (4.1)	7 (9.1)	.541
Neurologic complications	7 (6.6)	4 (6.6)	5 (6.8)	7 (9.1)	.913
Bacterial infection	10 (9.4)	6 (9.8)	17 (22.9)	23 (29.8)	.039
Dialysis dependence	10 (9.4)	11 (18.0)	7 (9.5)	22 (28.5)	.042

NOTE. Continuous variables presented as median and (interquartile range); categorical variables are presented as N (column %).
ACLF, acute-on-chronic liver failure.







Supplementary Table 1. Post-Transplant Infections According to ACLF Category

	No ACLF	ACLF-1, N = 7 (9.8%)	ACLF-2, N = 17 (22.9%)	ACLF-3, N = 23 (29.8%)
Infection site				
Skin/soft tissue	0	1	3	3
Spontaneous bacterial peritonitis	0	0	0	1
UTI	2	3	6	10
Bacteremia	0	2	5	5
Pneumonia	1	1	3	8
Organism				
ESBL *E coli*	0	3	4	5
VRE	0	1	2	4
C difficile	0	1	5	4
Pseudomonas	0	0	1	2
Klebsiella	2	0	2	2
E faecium	0	0	1	2
Staphylococcus epidermidis	0	1	1	1
MRSA	1	0	0	2
Fungal/Other	0	0	1	1

MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococcus.

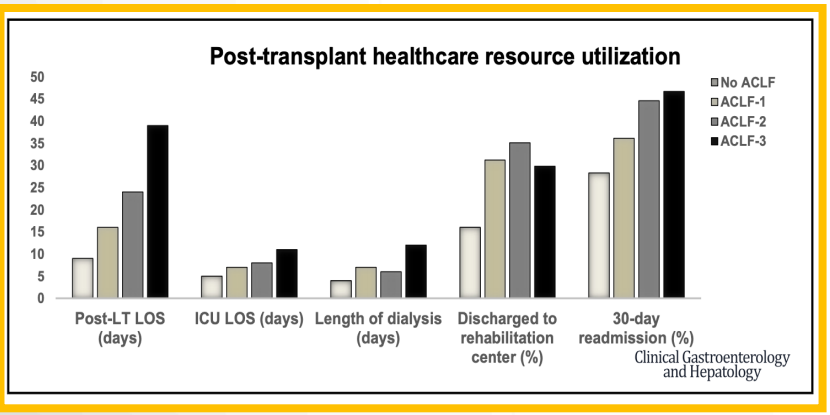


Table 3. Immediate Post-Transplant Resource Utilization, Categorized According to Severity of ACLF at Transplant[a]

	No ACLF	ACLF-1	ACLF-2	ACLF-3	*P* value
Length of hospital stay (*days*)	9 (4–19)	16 (11–40)	24 (12–40)	39 (19–94)	<.001
Length of ICU stay (*days*)	5 (3–14)	7 (4–18)	8 (3–14)	11 (4–17)	.202
Missing n, (%)	9 (8.5)	5 (8.2)	8 (10.8)	8 (10.4)	
Length of dialysis during hospitalization (*days*)	4 (2–11)	7 (3–21)	6 (3–20)	12 (4–22)	.037
Missing n, (%)[b]	1 (10.0)	2 (18.2)	0 (0.0)	2 (9.1)	
Disposition at discharge					<.001
Home	87 (82.1)	31 (50.8)	42 (56.8)	40 (51.9)	
Rehabilitation center	17 (16.0)	19 (31.2)	26 (35.1)	23 (29.8)	
Other	2 (1.9)	11 (18.0)	6 (8.1)	14 (18.2)	
30-day readmission	30 (28.3)	22 (36.1)	33 (44.6)	36 (46.7)	.042

Sundaram et al, Clinical Gastroenterology and Hepatology 2022