ACLF and Liver Transplantation

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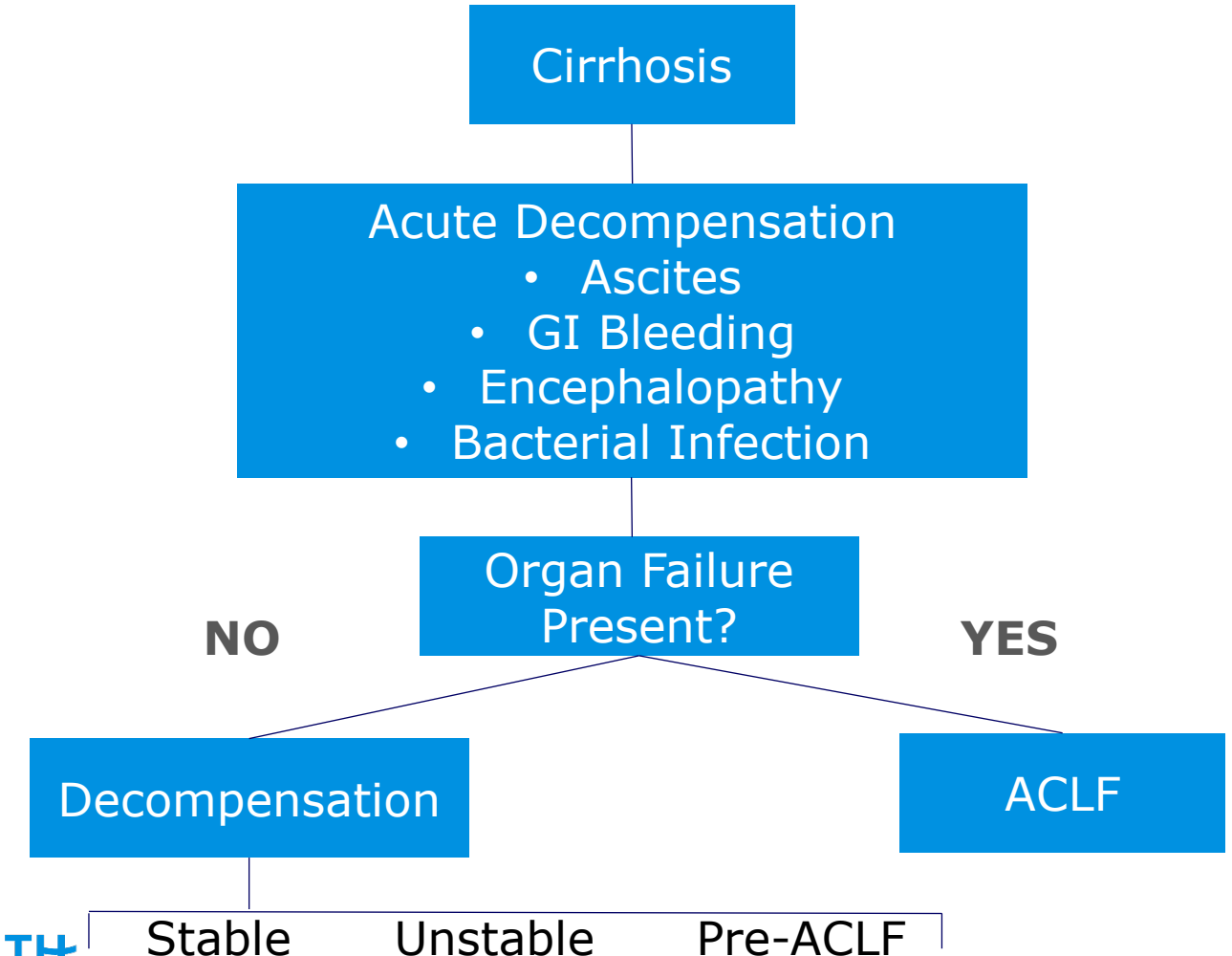
ACLF vs Decompensation in Cirrhosis



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ACLF: A Syndrome

- Acute decompensation in hospitalized patients with cirrhosis
  - New onset HE
  - Recent onset of ascites
  - GI bleeding
  - Infection
- Intense systemic inflammatory response
- Single or multiple organ failure
- Close association with precipitating event
  - Infection
  - Alcohol associated hepatitis
- High 28 day mortality

What Is ACLF Grading and CLIF-SOFA Score?

ACLF

- ACLF describes the syndrome characterized by acute decompensation of cirrhosis, organ failure, and high short-term mortality[1]
  - Seen in ~30% of patients with decompensated cirrhosis[1]
  - Can be triggered by sepsis, alcohol use, and the relapse of chronic viral hepatitis, as well as many unidentifiable causes[2]
  - Thought to develop via an excessive systemic inflammatory response[2]

Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) Score

- CLIF-SOFA score was developed to predict mortality risk in patients with ACLF[1,2]
  - Using this scoring system, patients are categorized as being ACLF grade 1, 2, or 3 based on the number of organ system failing[2]
  - Higher ACLF grades are associated with higher mortality[2]

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1. Jalan R et al. *J Hepatol.* 2014;61(5):1038-1047.
2. 2. Hernaez R et al. *Gut.* 2017;66(3):541-553

ACLF is Different than Acute Decompensation

- ACLF has
  - Higher mortality
  - More alcohol, infection or more than one trigger
  - More inflammation
  - Differences in metabolic reprogramming
  - Abnormal mitochondria
  - Change in microbiome

O'Leary JG, Hepatology 2018;67(6):2367-74, Moreau, Gastro 2013;144(7):1426-37, Tribicka, J Hep 2021;74(5):1097-1108, MacDonald, Hepatology 2018;67(3):989-1002, Zaccherini, J Hep 2021;74(5):1117-1131, Zhang, J Hep 2022;76(1):93-106, Sole, Gastro 2021;160(1):206-18

ACLF: Multiple Organ Failure Definitions

- Syndrome Characterized by high short-term mortality in patients with cirrhosis associated with hepatic +/- extrahepatic organ failure

	NACSELD	EASL-CLIF	APASL AARC
Liver		**Bilirubin ≥ 12 mg/dL**	**Bilirubin ≥ 15 mg/dL**
Kidney	**RRT**	**Cr ≥ 2 mg/dL or RRT**	**Cr ≥ 1.5 mg/dL**
Brain (HE)	**III-IV**	**III-IV**	**I-IV**
Circulatory	**Inotropes**	**Inotropes**	**Lactate ≥ 1.5**
Respiratory	**BiPAP/Ventilator**	**BiPAP/Ventilator**	
Coagulation		**INR ≥ 2.5**	**INR ≥ 1.8**

Hernaez R, GUT 2017;66(3): 541-3

CLIF-SOFA Score

Organ System	Variable			
Liver	Bilirubin (mg/dl)	< 6.0	≥ 6 to < 12	≥ 12
Kidney	Creatinine (mg/dl)	< 2.0	≥ 2.0 to < 3.5	≥ 3.5 or RRT
Cerebral	HE grade (West Haven criteria)	0	I-II	III-IV or intubation for HE
Coagulation	INR	< 2.0	≥ 2.0 to < 2.5	≥ 2.5
Circulation	MAP (mm Hg)	≥ 70	< 70	Use of vasopressors
Respiration	PaO2/FiO2 SpO2/FiO2	> 300 > 357	>200 to ≤ 300 > 214 to ≤ 357	≤ 200 ≤ 214 Or use of mechanical ventilation

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Zaccherini G, JHEP Reports 2020;3(1):100176
Moreau, Gastro 2013;144(7):1426-37

ACLF Definitions

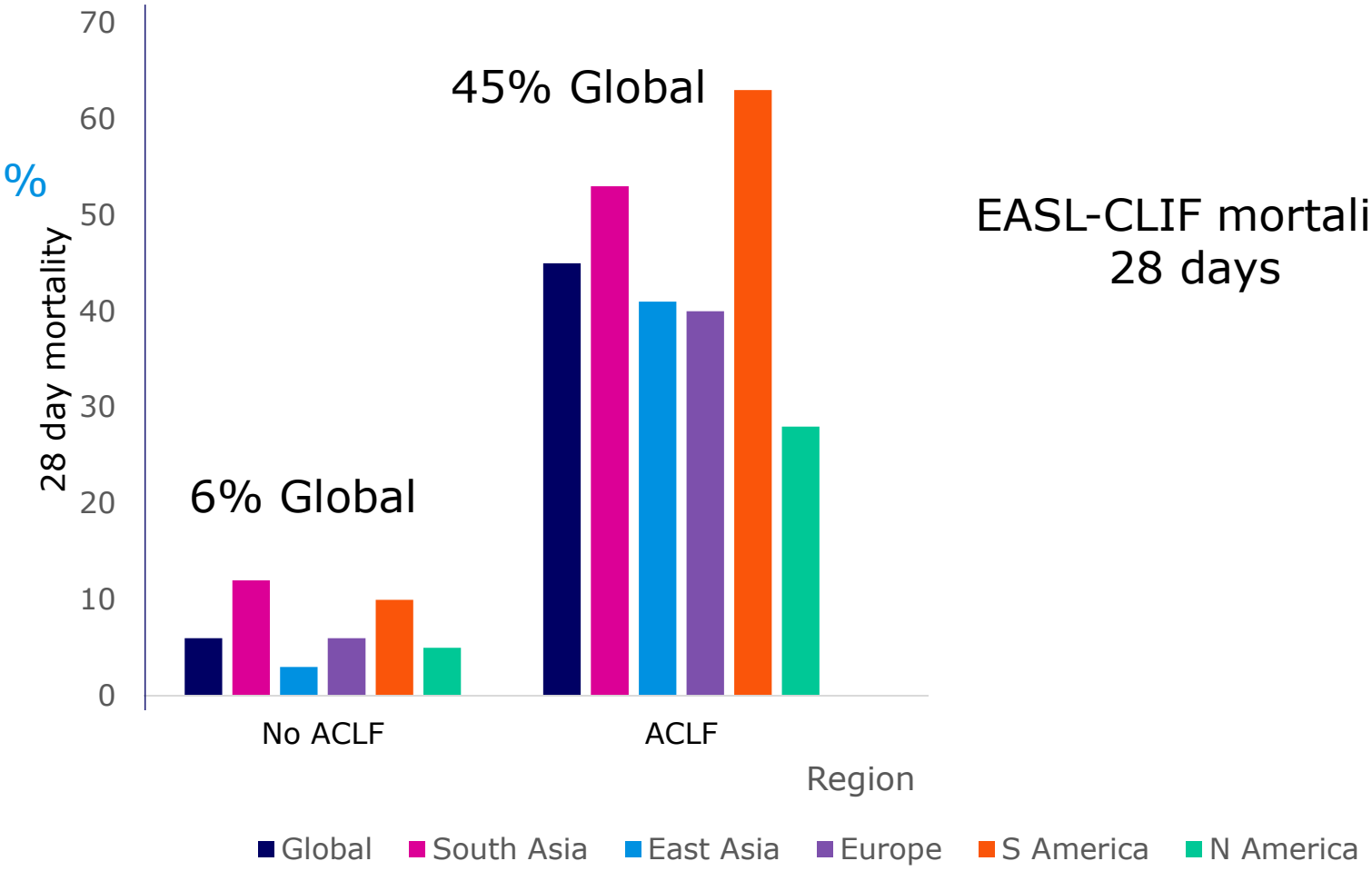
- ACLF 1
  - Single organ kidney failure
  - Single liver, coag, circulatory or lung failure with Cr 1.5-1.9 or HE grade 1 or 2 or both
  - Single brain failure with cr 1.5-1.9
- ACLF 2
  - 2 organ failures
- ACLF 3
  - 3 organ failures

Guardia BD, World J Gastroenterol 2022

Acute Decompensation Mortality Lower than ACLF

Triggers
- Bacterial infection 35%
- GIB 22%
- Acute alcohol 19%

Kidney dysfunction
Most common organ
Failure 49%



EASL-CLIF mortality
28 days

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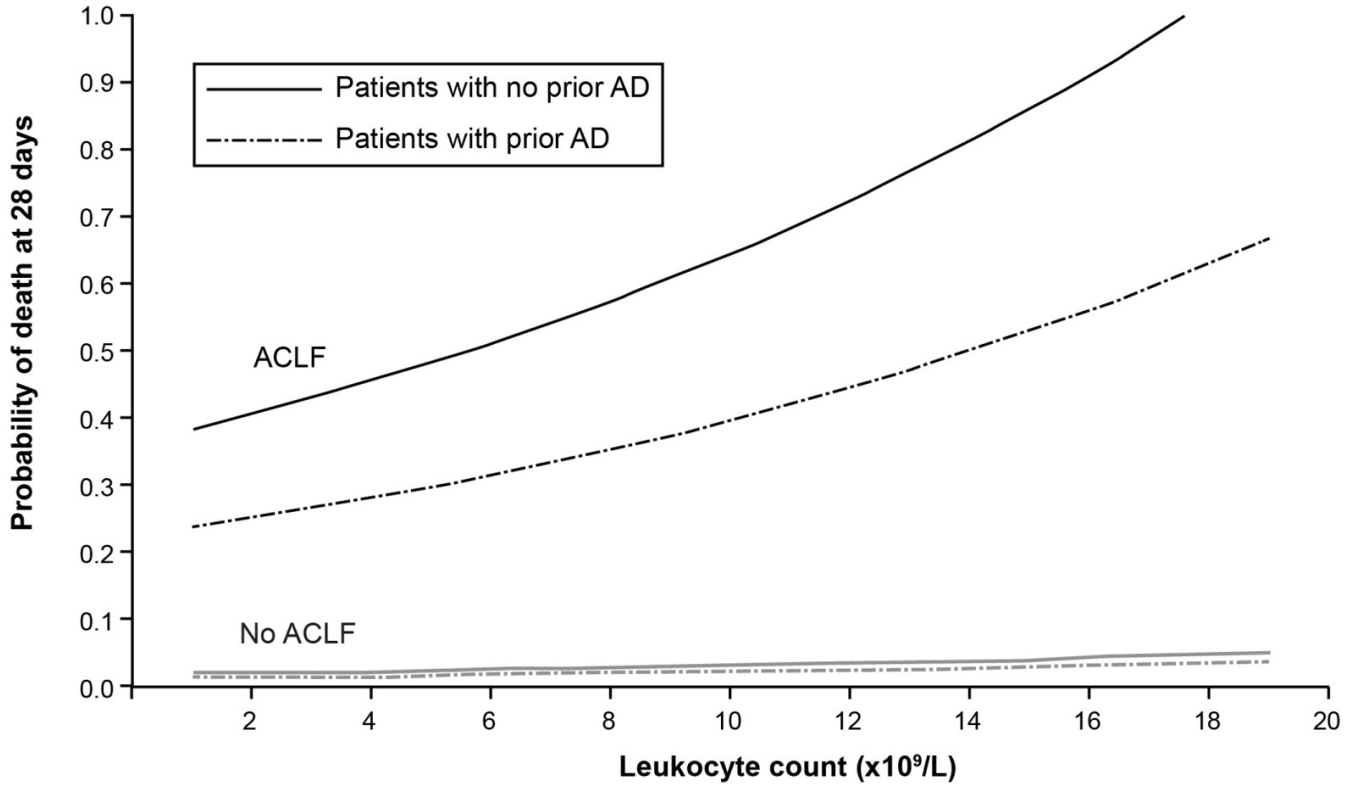
Mezzano et al, Gut 2022;71(1):148-55

Relationship between probability of death at 28 days and leukocyte count according to Presence of ACLF and prior history of AD



Moreau et al. Gastroenterology 2013; 144(7):1426-1437.

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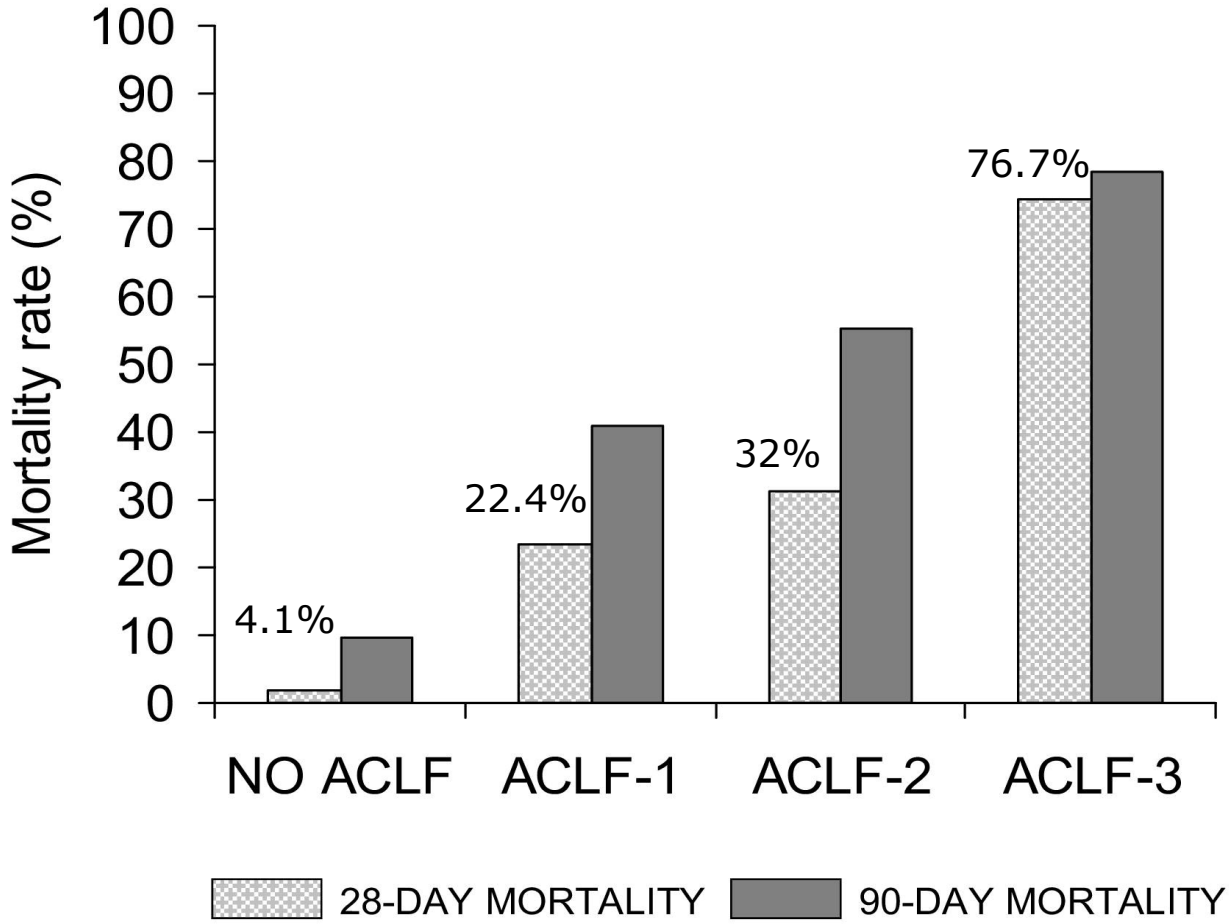
Mortality Based on ACLF Grade



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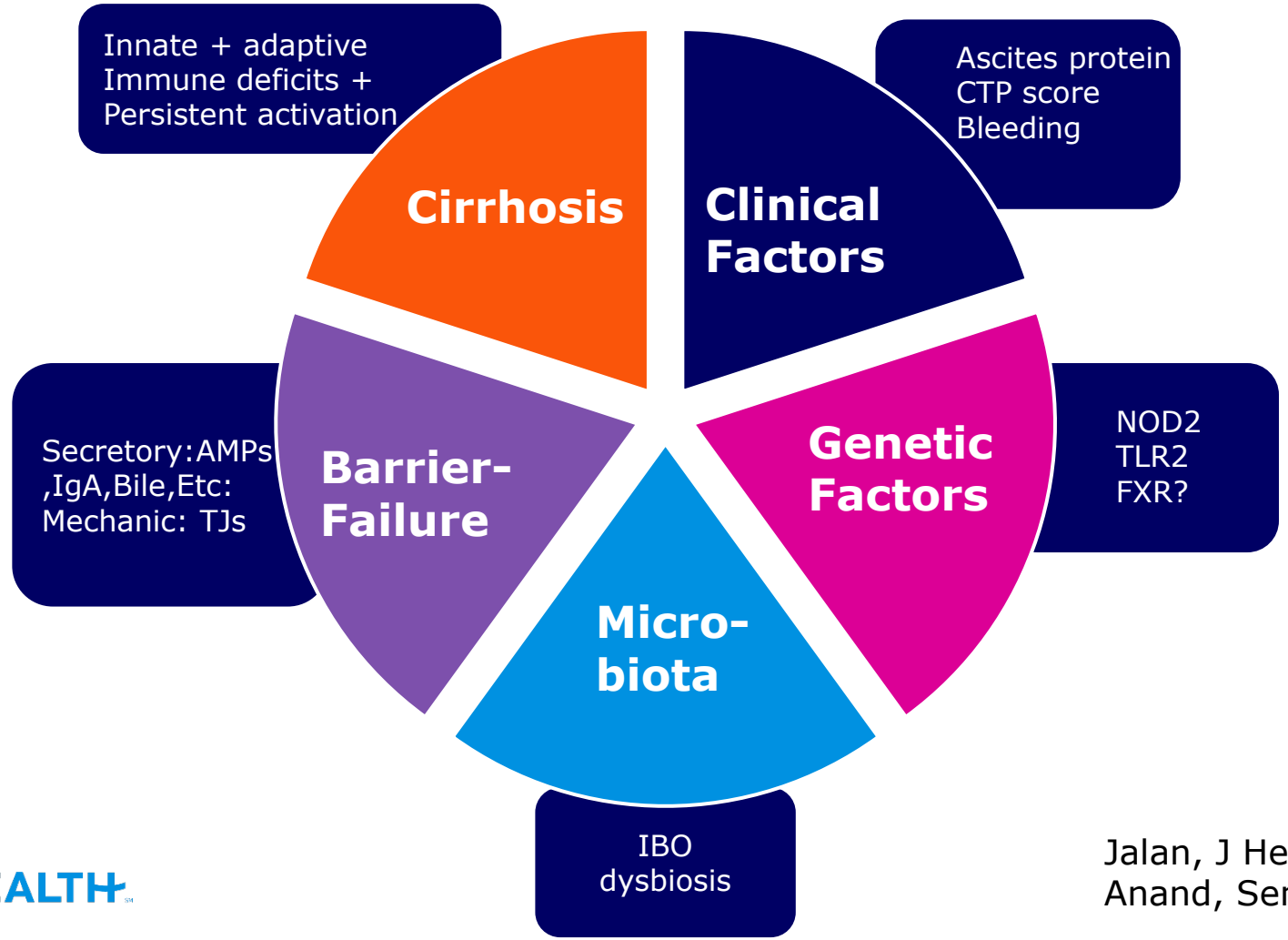
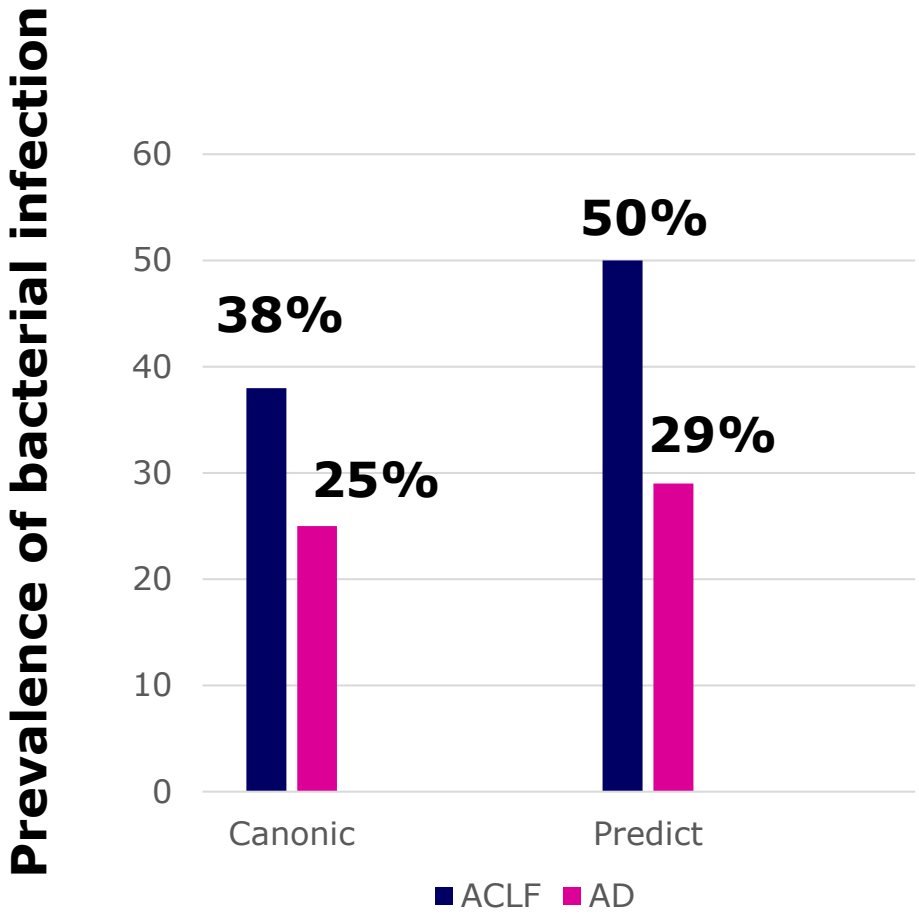
Moreau et al. Gastroenterology 2013; 144(7):1426-1437.

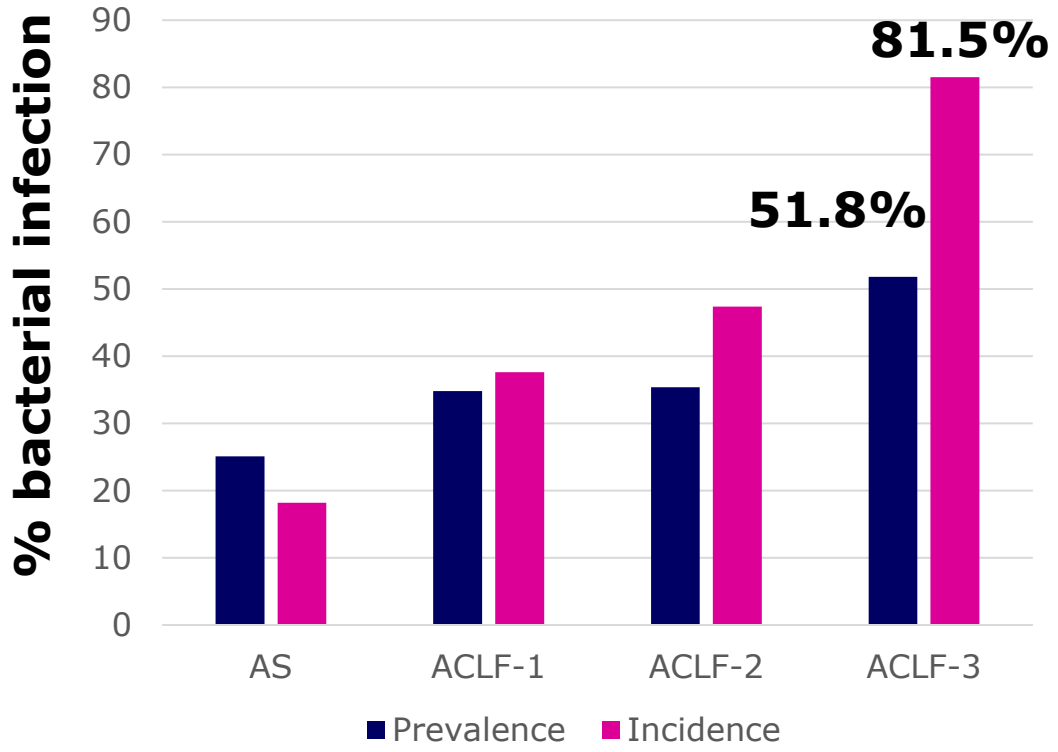
Bacterial Infection in Cirrhosis



Jalan, J Hep 2014
Anand, Semin Liver Dis 2016

Prevalence and Incidence of Bacterial Infection in ACLF





Moreau, Gastro 2013,
Trebicka, J Hep 2022
Fernandez, Gut 2018

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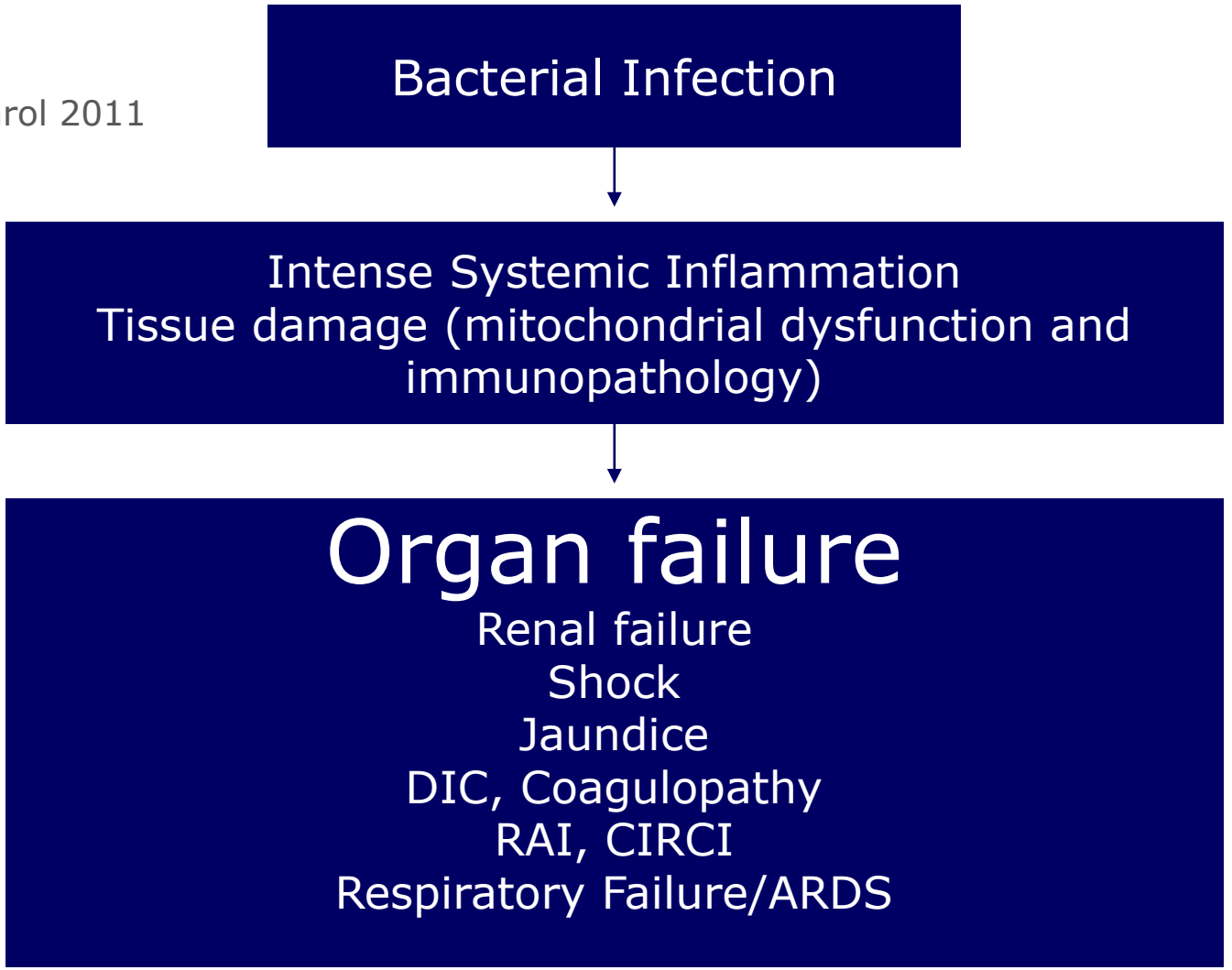
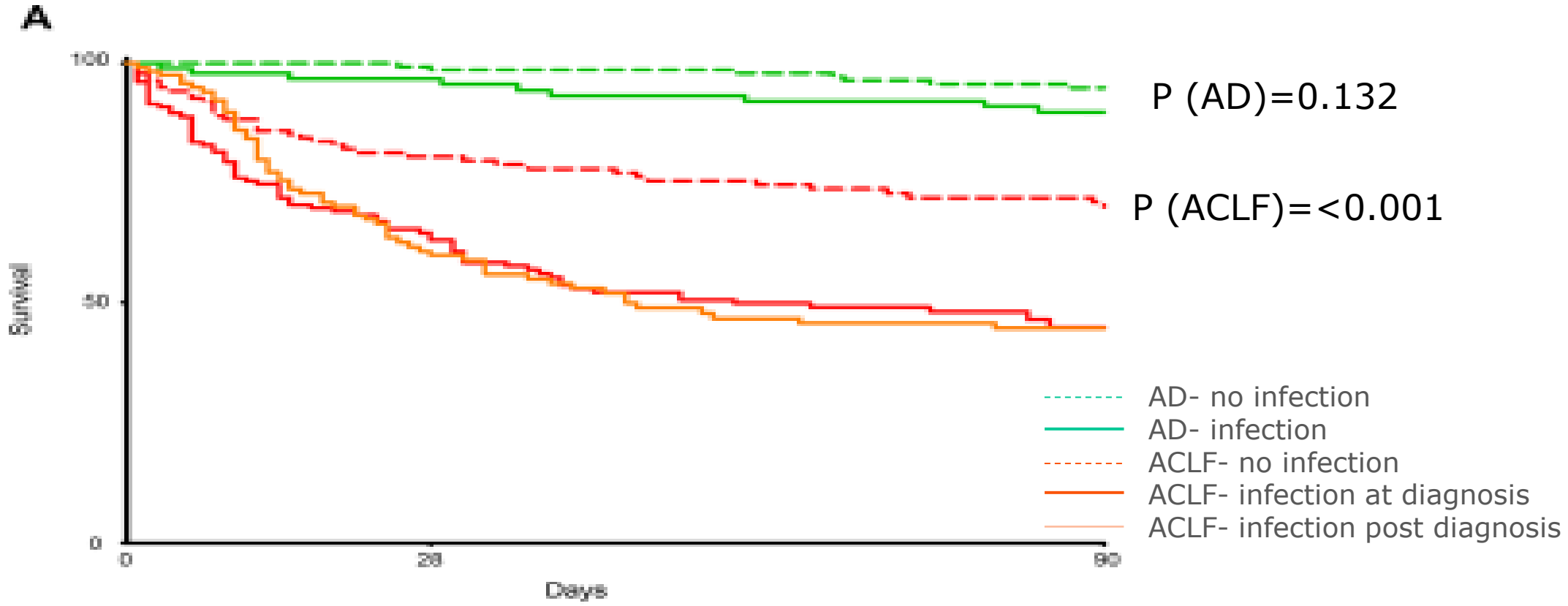
Pathogenesis of ACLF: Impact of Infection

Arroyo, Nat Rev Nephrol 2011



90 Day Transplant –Free Survival AD and ACLF



Fernandez, Gut 2018

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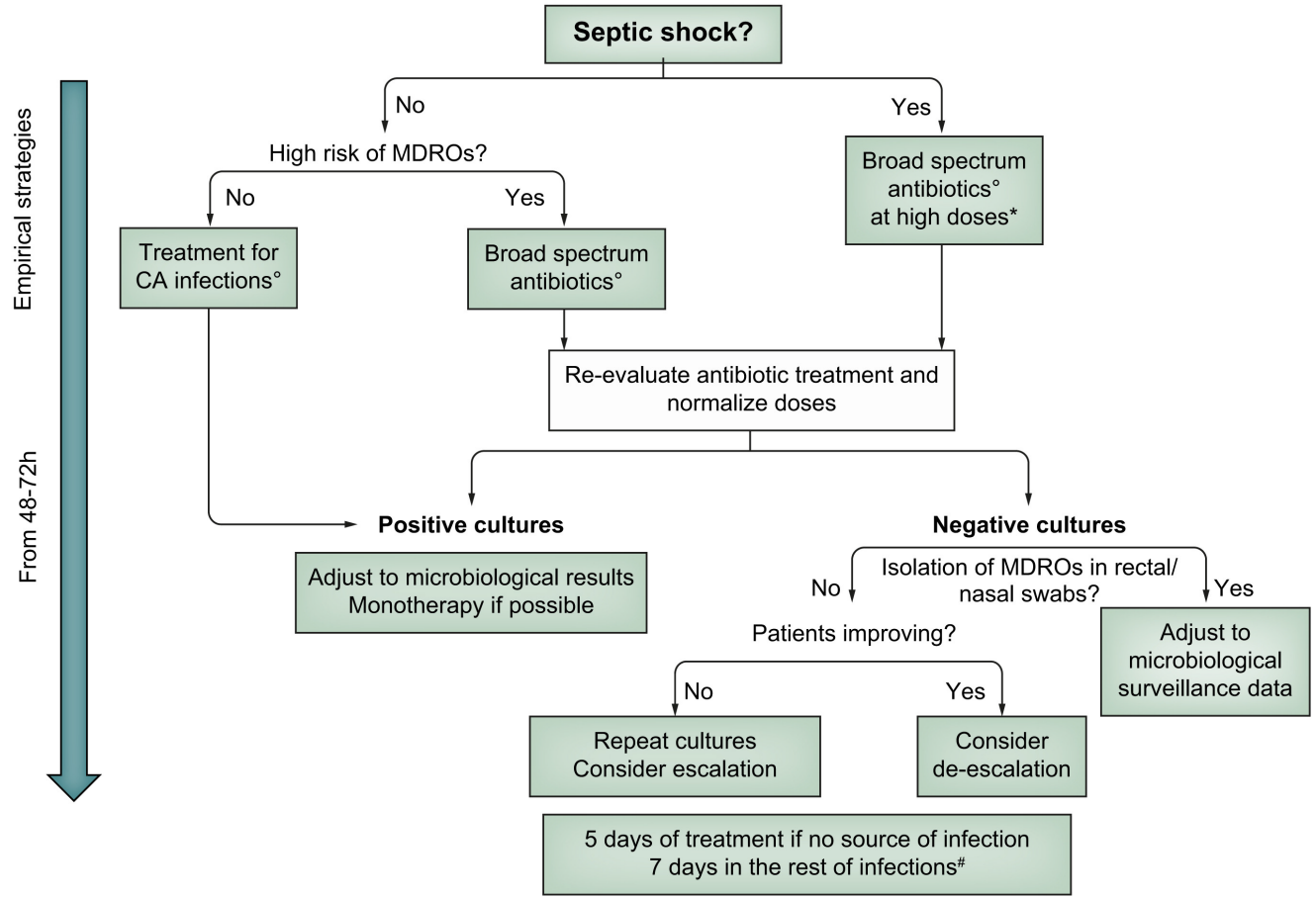
Algorithm for Management Cirrhosis and Sepsis



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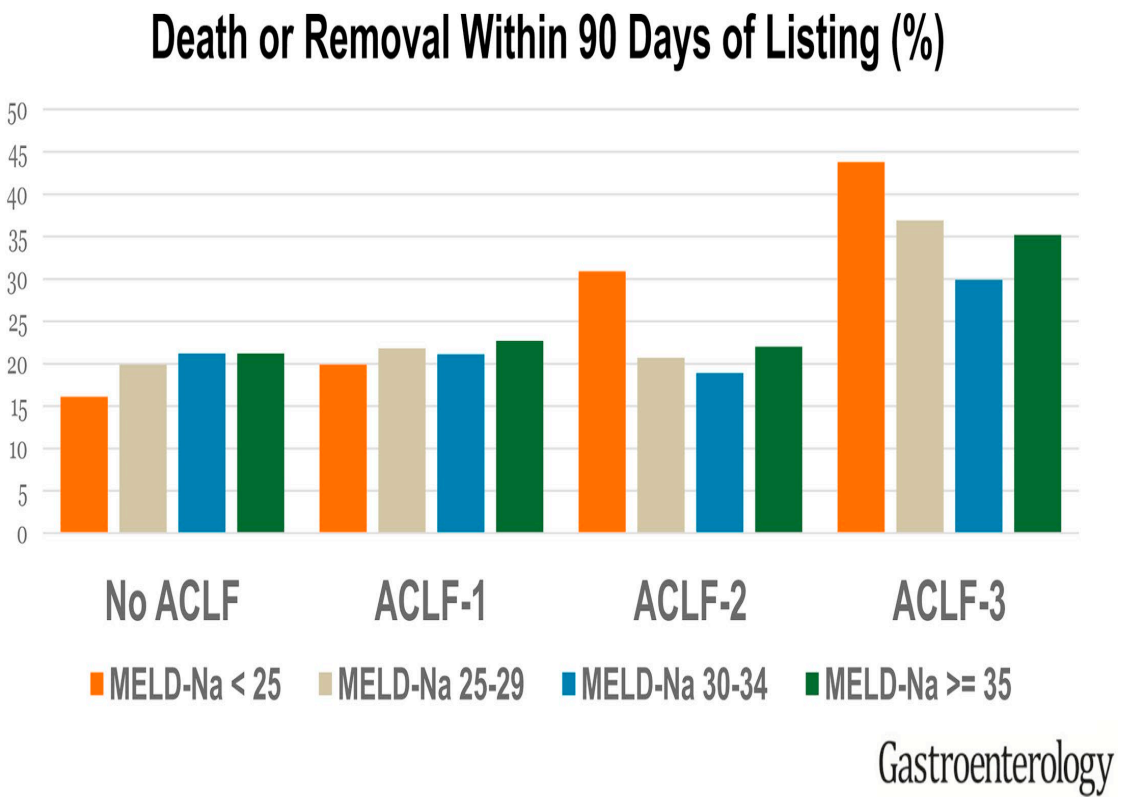
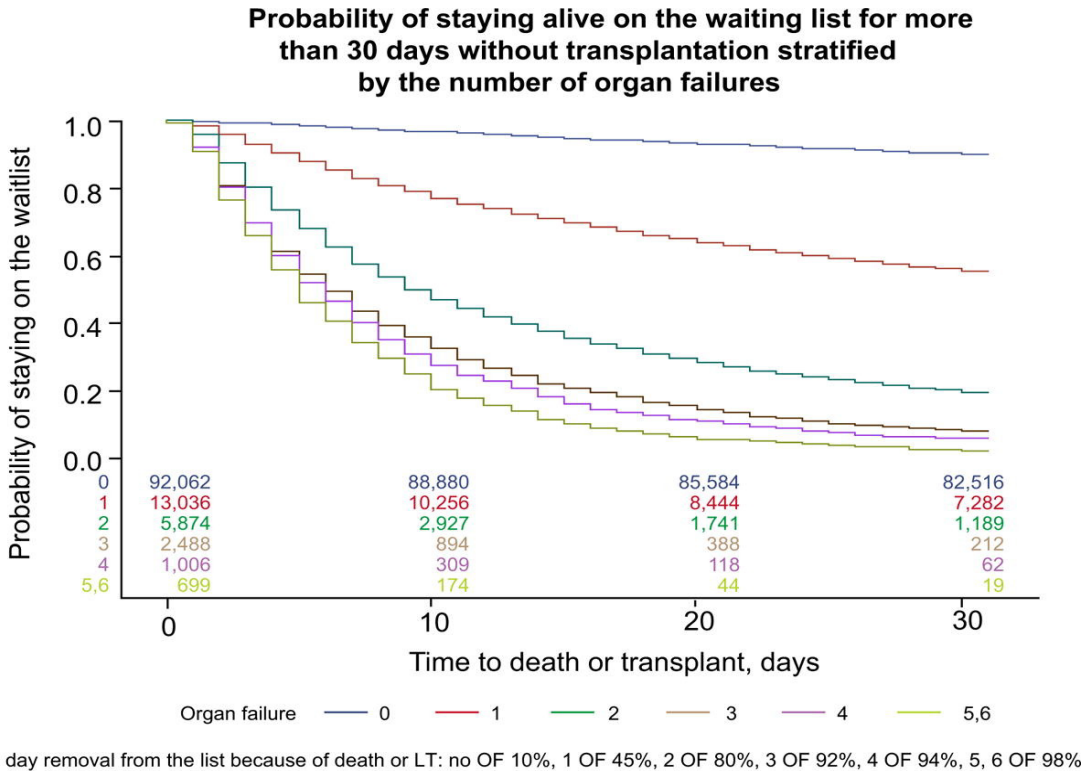
Fernandez, J Hep 2021

Liver Transplant for ACLF

- Urgency
- Utility
- Equity

Waitlist Mortality in Patients with ACLF





Sundaram, Gastro 2019, Thuluvath, J Hep 2018

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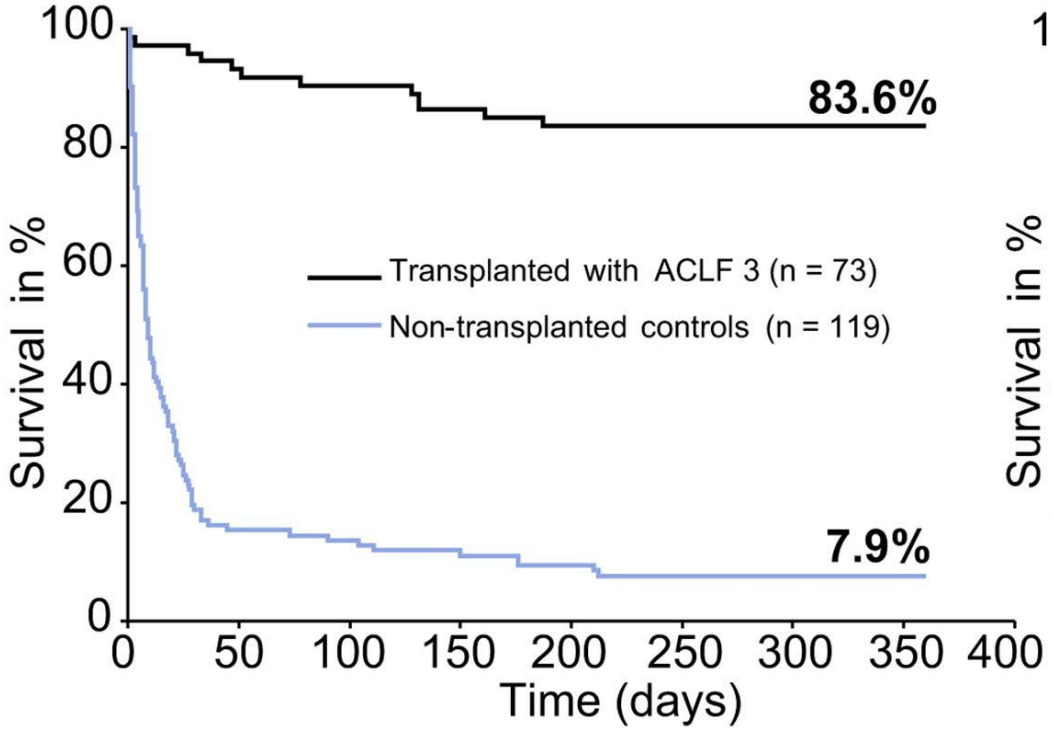
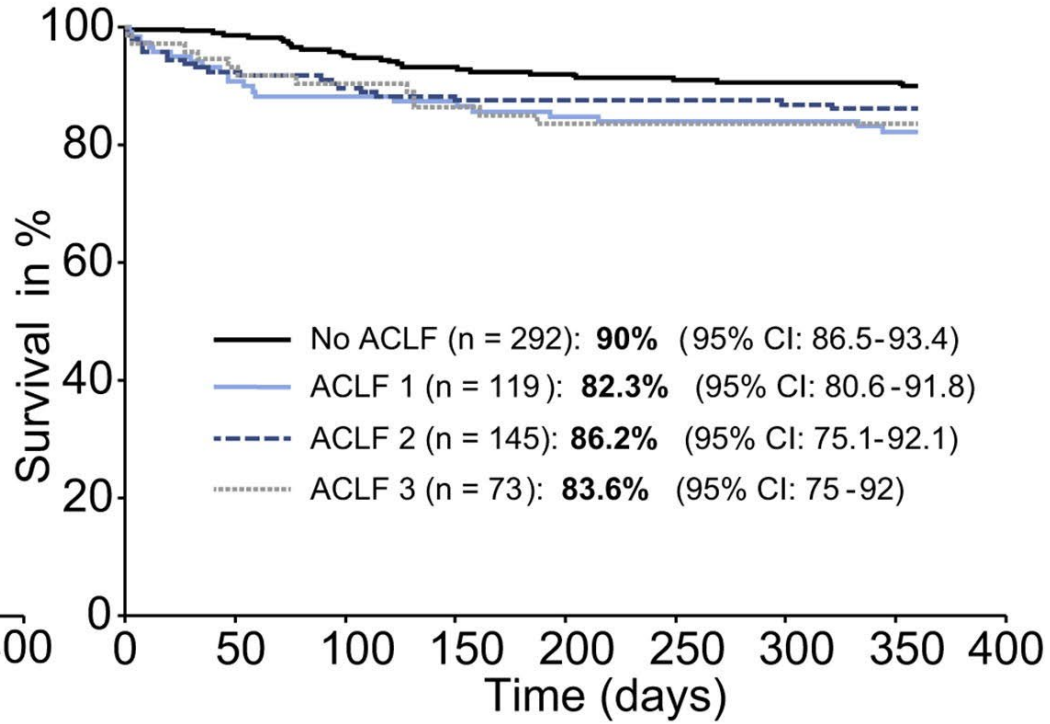
Survival Benefit of Liver Transplant in ACLF3





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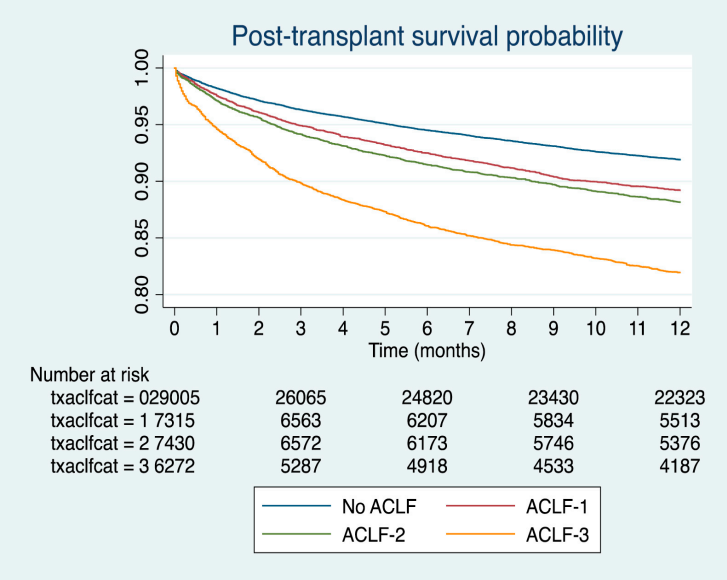
Artu, J Hep 2017

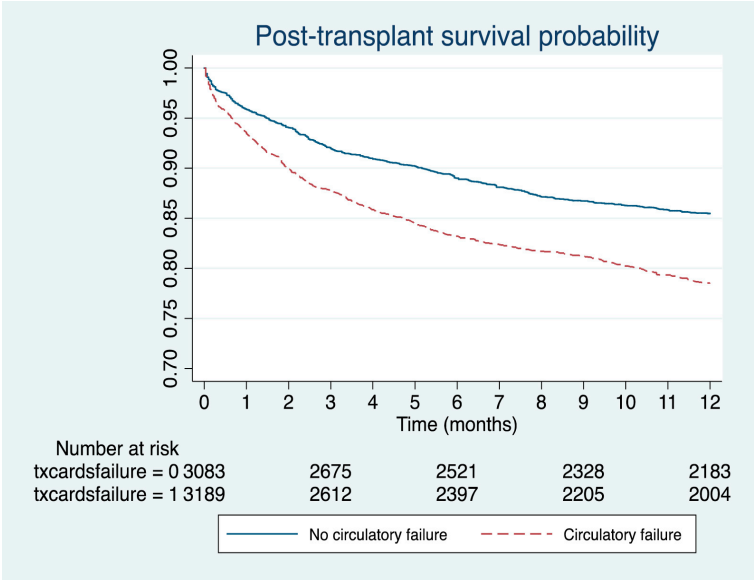
Independent Predictors of 1-Year Patient Survival with ACLF3 at Listing

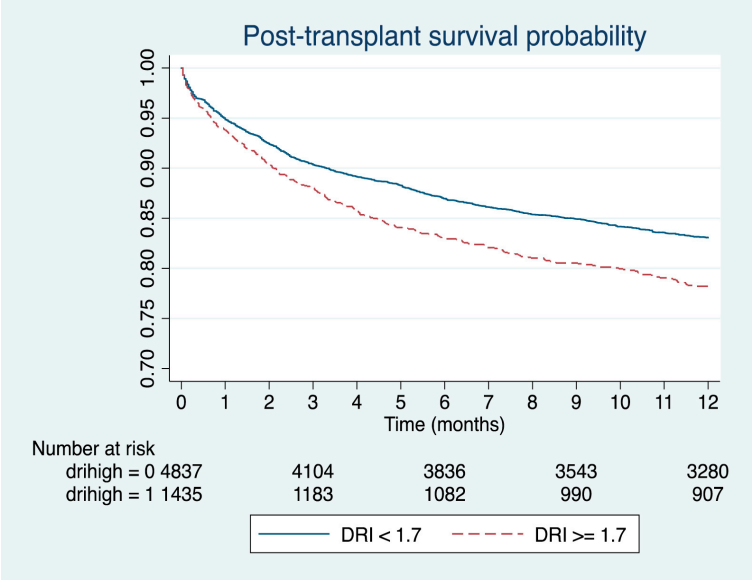
Covariates	Hazard Ratio (95% CI)
Karnofsky score ≥ 80	0.76 (0.55-1.06)
Futility Score > 8 (ventilator, age > 60, Cr >1.5, DM, RRT)	1.12 (0.97-1.30)
Circulatory Failure	0.90 (0.78-1.05)
> 3 organ failure	1.04 (0.92-1.19)
Transplant within 30 days of listing	0.89 (0.81-0.98)
DRI ≥ 1.7	1.22 (1.09-1.35)
Mechanical Ventilation	1.49 (1.22-1.84)

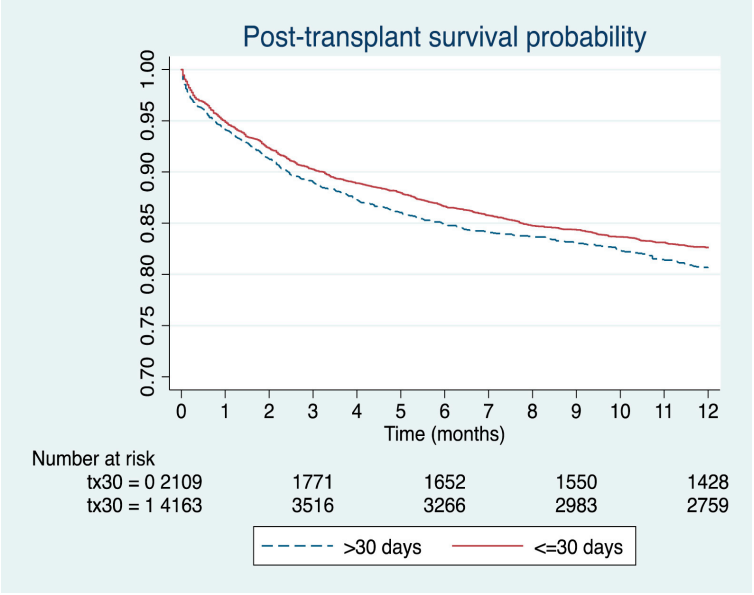
Sudaram, Gastro 2019

Factors Affecting 1 Year Survival Post OLT in Patients with ACLF









Sudaram, Gastro 2019

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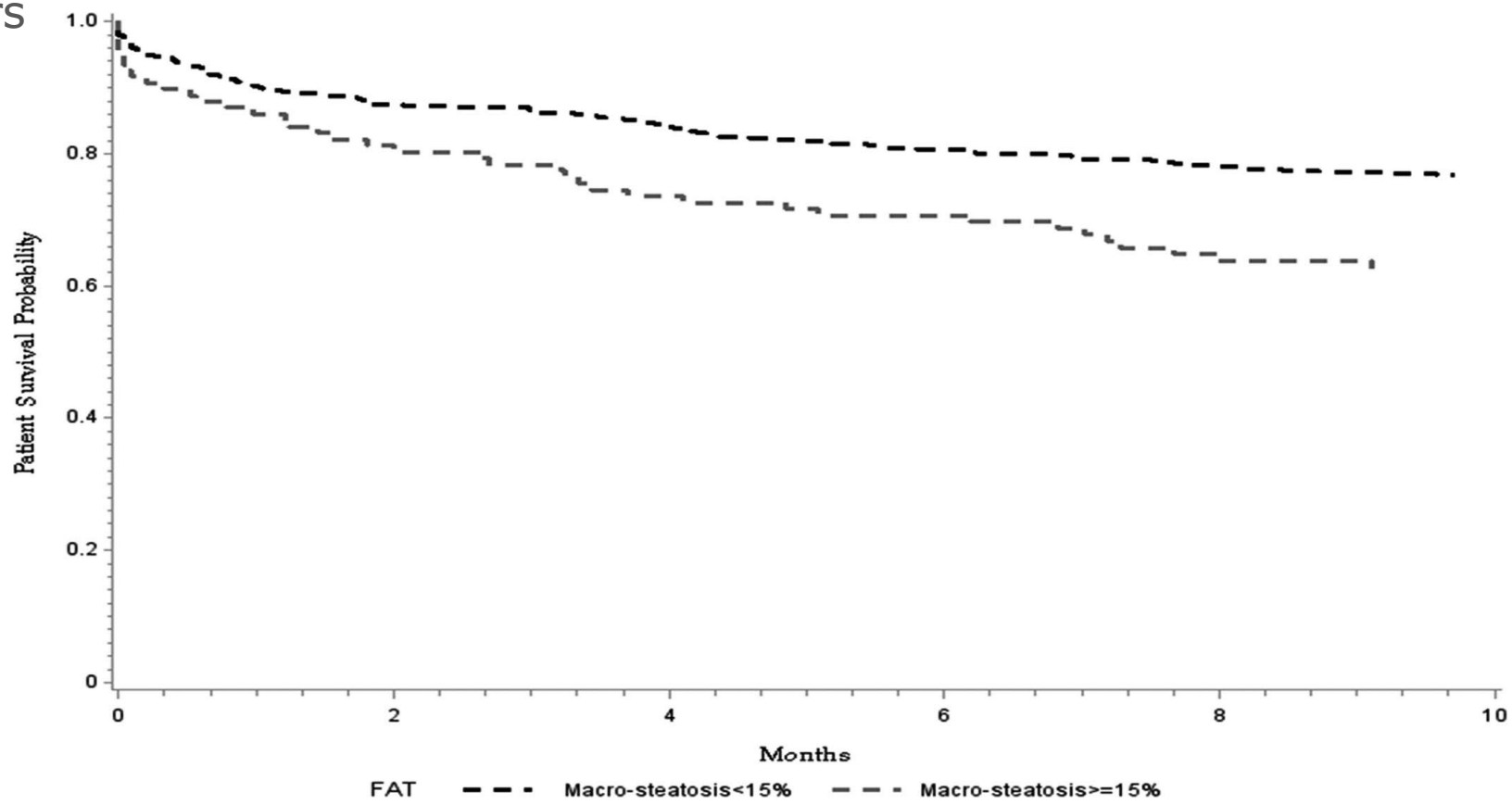
Survival in High Risk Recipients Comparing Graft Steatosis

UNOS Jan 2002- June 2018
54,956 LT recipients of which 43.6% had ACLF at time of LT

Independent predictors
Recipient age
Pulmonary failure
Brain failure
CV failure
Alcohol liver disease

Tertiles
Low risk < 7.55
Medium 7.55-11.57
High risk > 11.57



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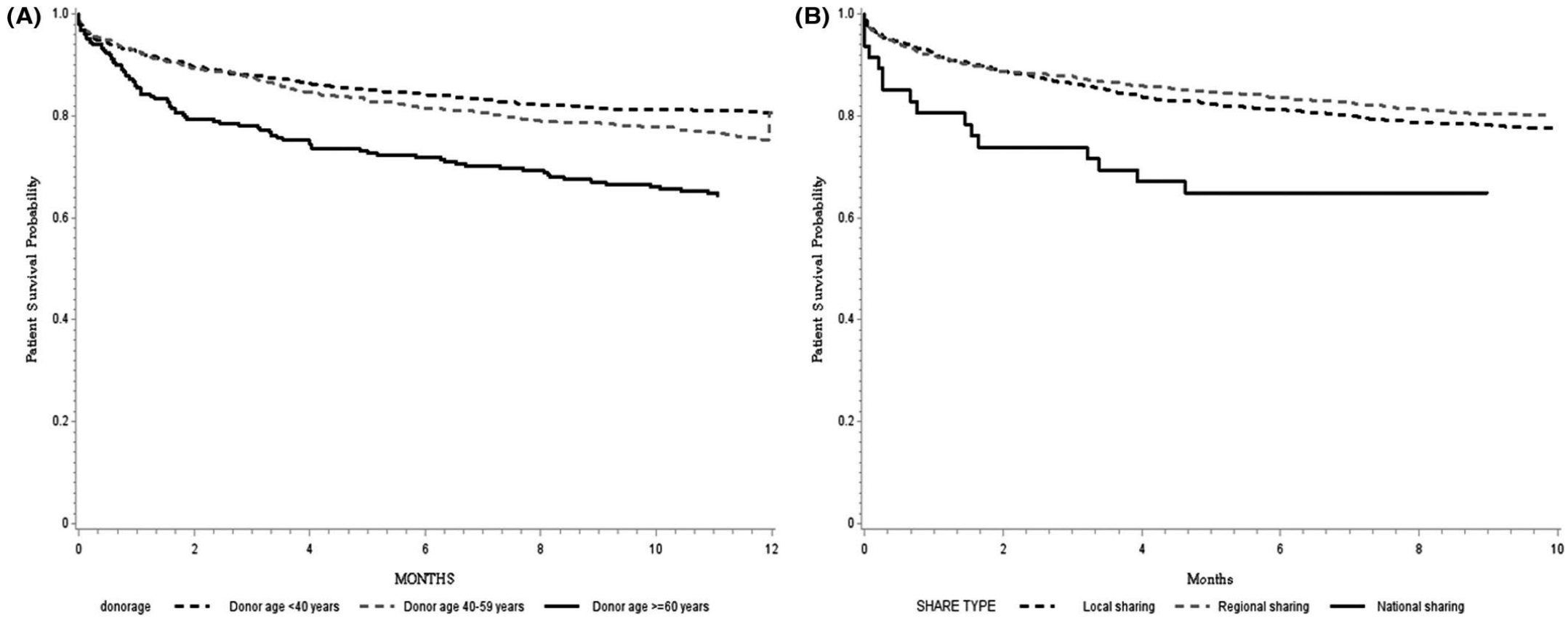
Singal, Liver International 2022

Survival in High Risk Recipients Comparing Donor Age and Local vs Regional/National Sharing



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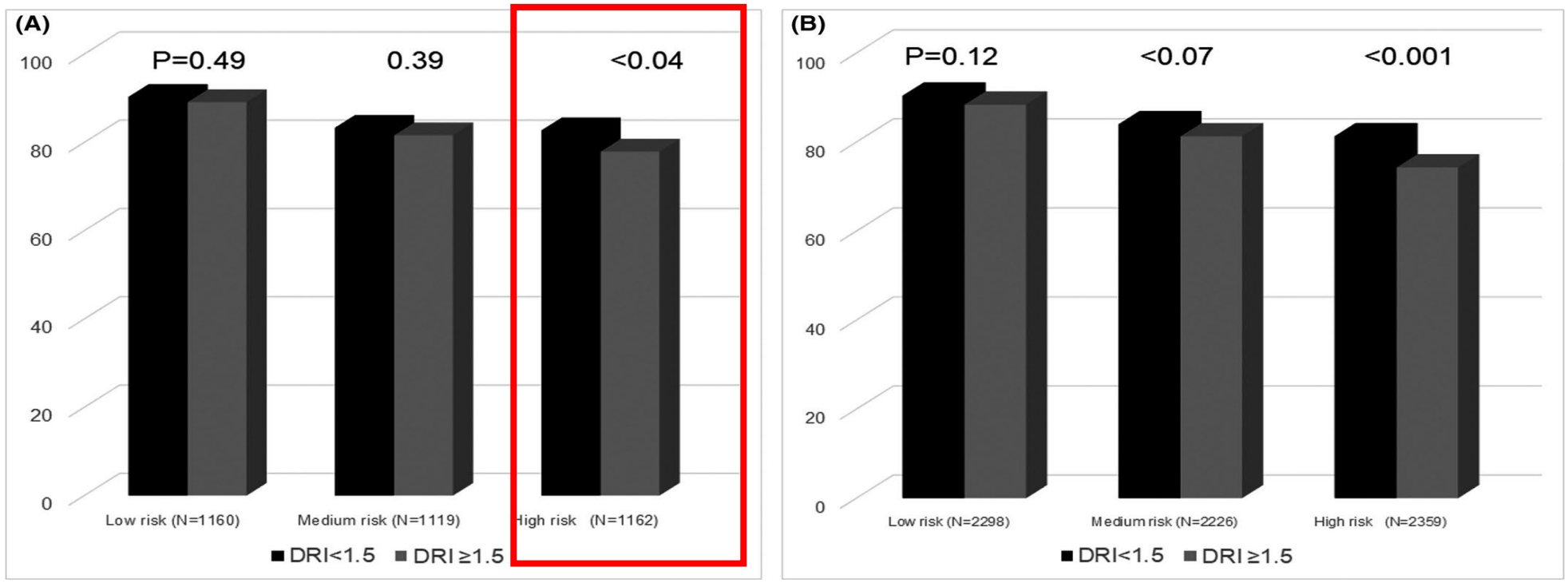
Singal, Liver International 2022

High-risk liver transplant recipients with ACLF 3 should receive the good quality graft

UNOS Jan 2002- June 2018
54,956 LT recipients of which 43.6% had ACLF at time of LT

Validation **Whole Dataset**



Singal, Liver International 2022

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Transplant Outcomes Research for ACLF using Registry Data: Limitations

- Acute decompensation
  - –Recent onset ascites
  - –New onset HE
  - –GIB x
  - –Infection X

Does not distinguish between new or existing

- Organ Failure
  - –Circulatory failure/ pulmonary failure at listing x
  - –He grade at listing
- Misclassification

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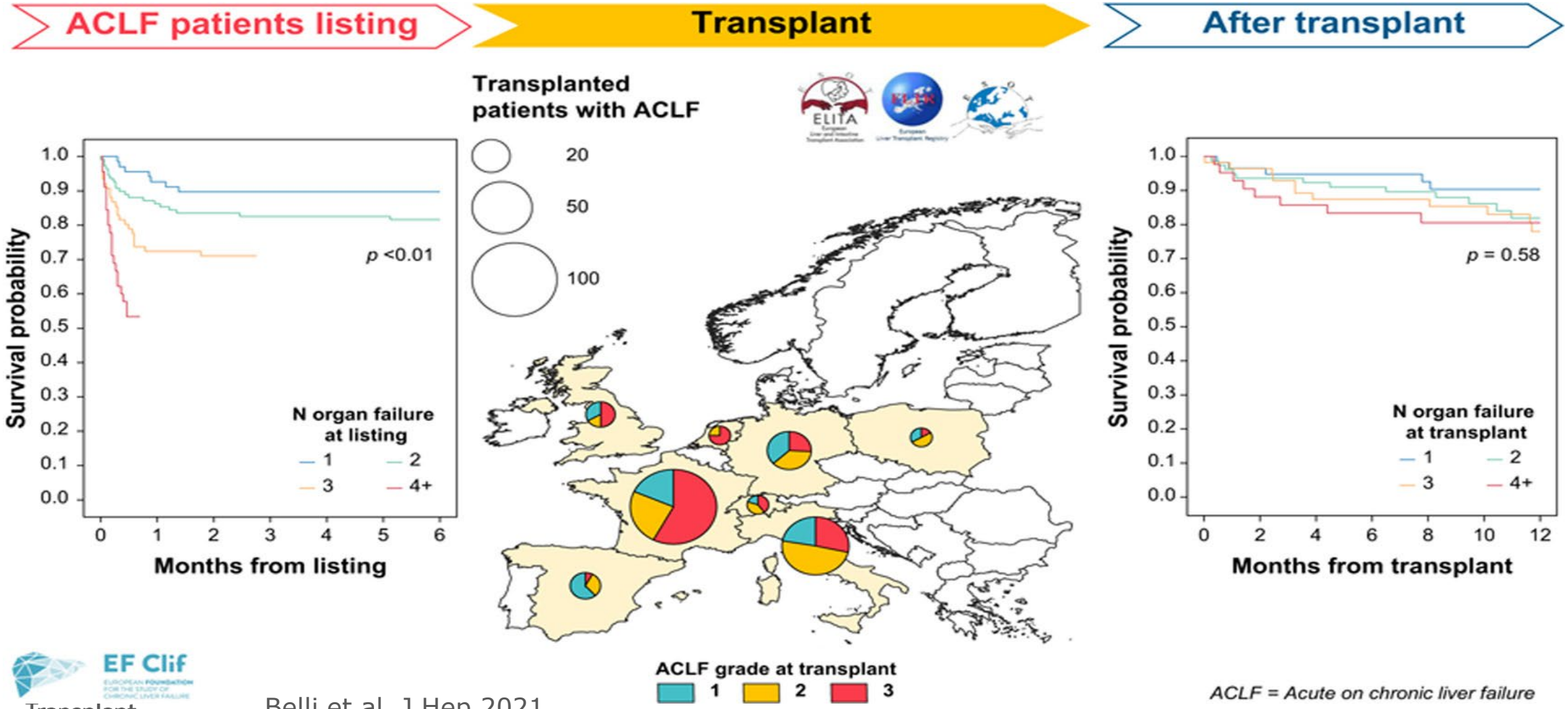
Independent Predictors of Post-Transplant Mortality: Results of the ELITA/EFCLIF Collaborative Study (ECLIS)



ACLF = Acute on chronic liver failure

Belli et al, J Hep 2021

Independent Predictors of Post Transplant Mortality

Covariates2	Hazard Ration (95% CI)	P-Value
Dialysis	2.74 91.37-5.51)	0.005
Lactate > 4 mmol	3.14 (1.37-7.19)	0.007
MDR infection	3.67 (1.63-8.28)	0.002

Belli et al, J Hep 2021 (European)

Covariate	Odds Ratio	P-Value
Age > 50 years	2.24	0.01
1 vasopressor	1.80	0.09
> 1 vasopressor	4.05	<0.001
Mechanical Ventilation	2.03	0.019
MDR Bacteria	1.90	0.02

15 LT centers
2014-2019
(n=521)

US

Model score
Superior to MELD

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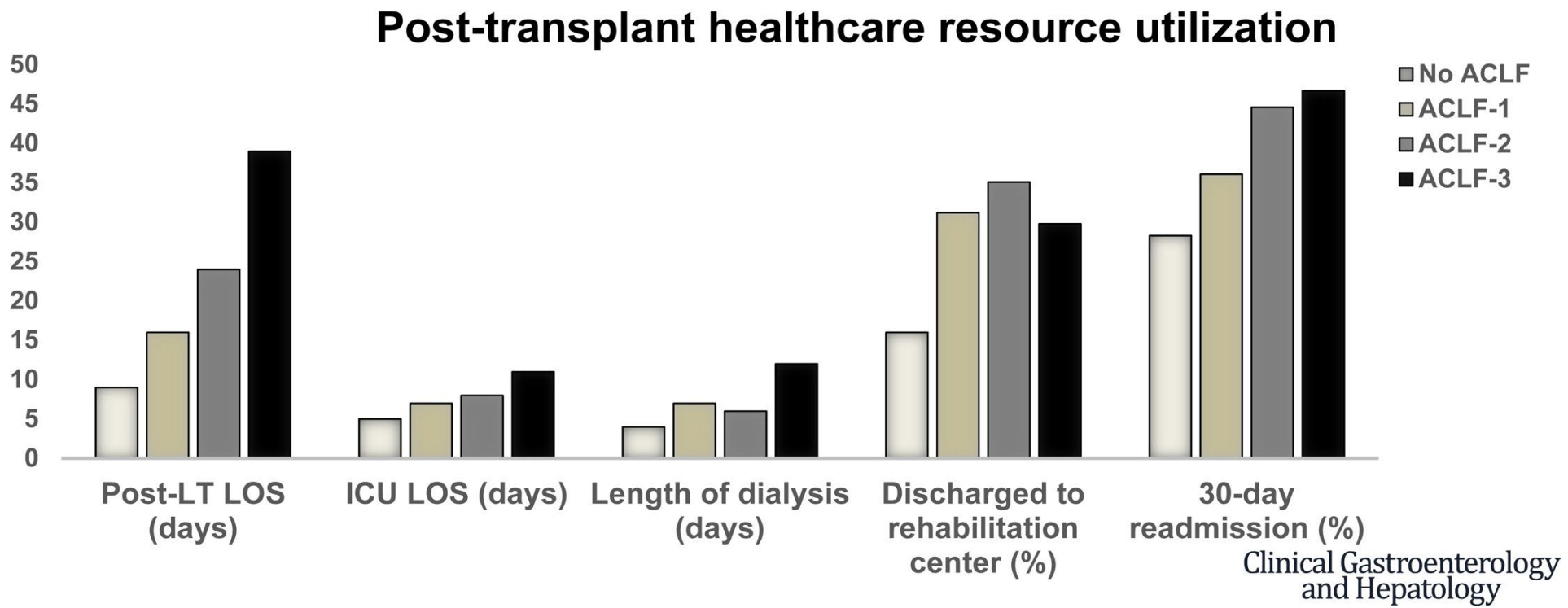
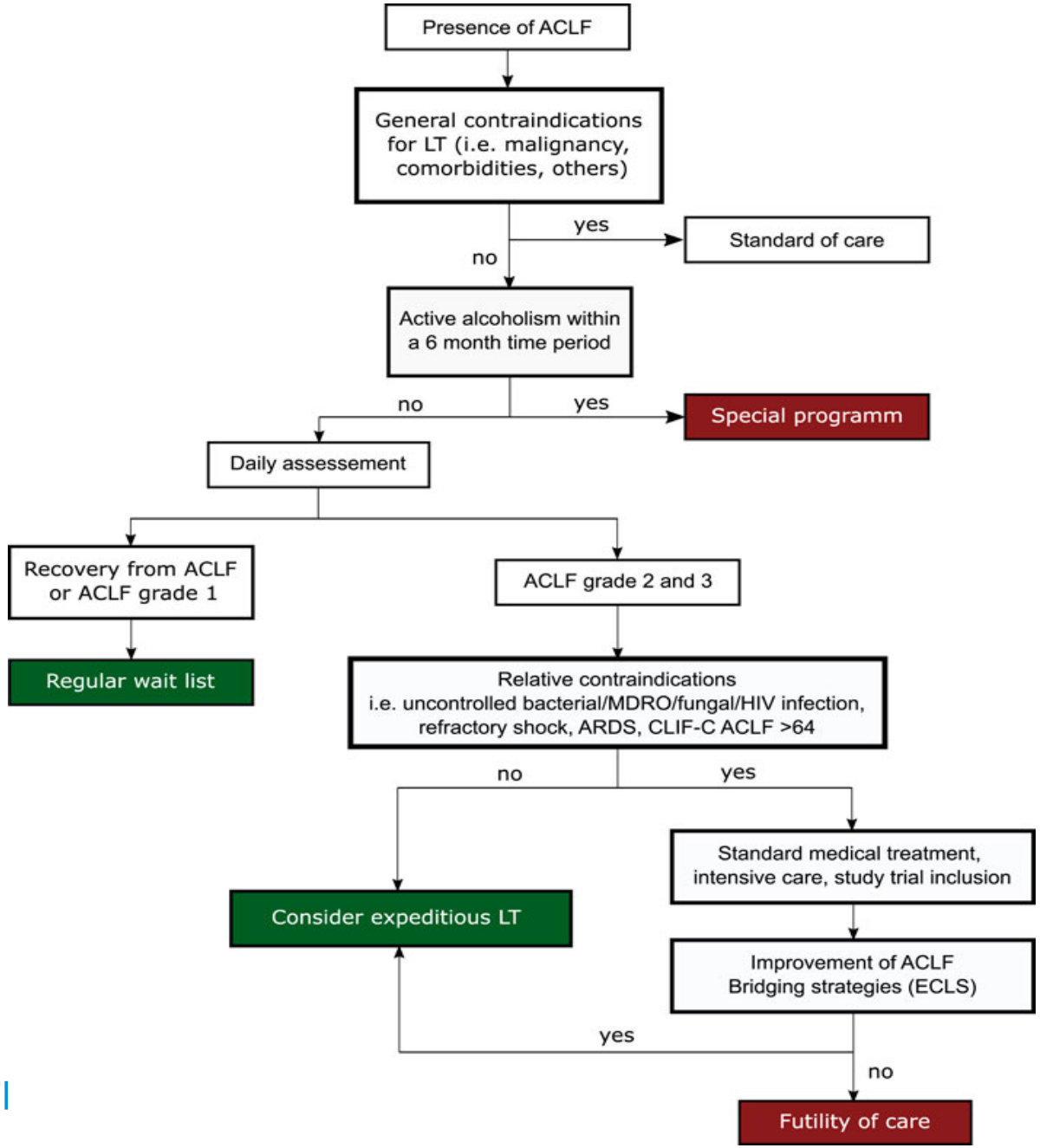
Sundaram, Hepatology 2022 (S74, Abstract #4)

Resource Utilization



Sundaram, CGH 2022



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Conclusions

- ACLF is a distinct entity different from but related to Acute Decompensation in patients with cirrhosis
- Precipitating factors include infection, acute alcohol use most common
- Degree of ACLF influences outcomes
- Liver Transplantation provides survival benefit in patients with ACLF including those with ACLF3
- Post transplant survival is lower in ACLF3 compared with those with ACLF 1 or 2 or no ACLF
- Patients with ACLF have greater post transplant resource utilization
- Careful patient and donor organ quality selection is key for optimal outcomes
- Early recognition and transfer to a liver transplant center is critical