

Acute on Chronic Liver Failure: The Role of Liver Transplantation

Vinay Sundaram, MD, MSc, FACP
Associate Professor of Medicine
Director, Hepatology Outcomes Research
Cedars-Sinai Medical Center

Disclosures

Advisory board/consulting: Saol therapeutics

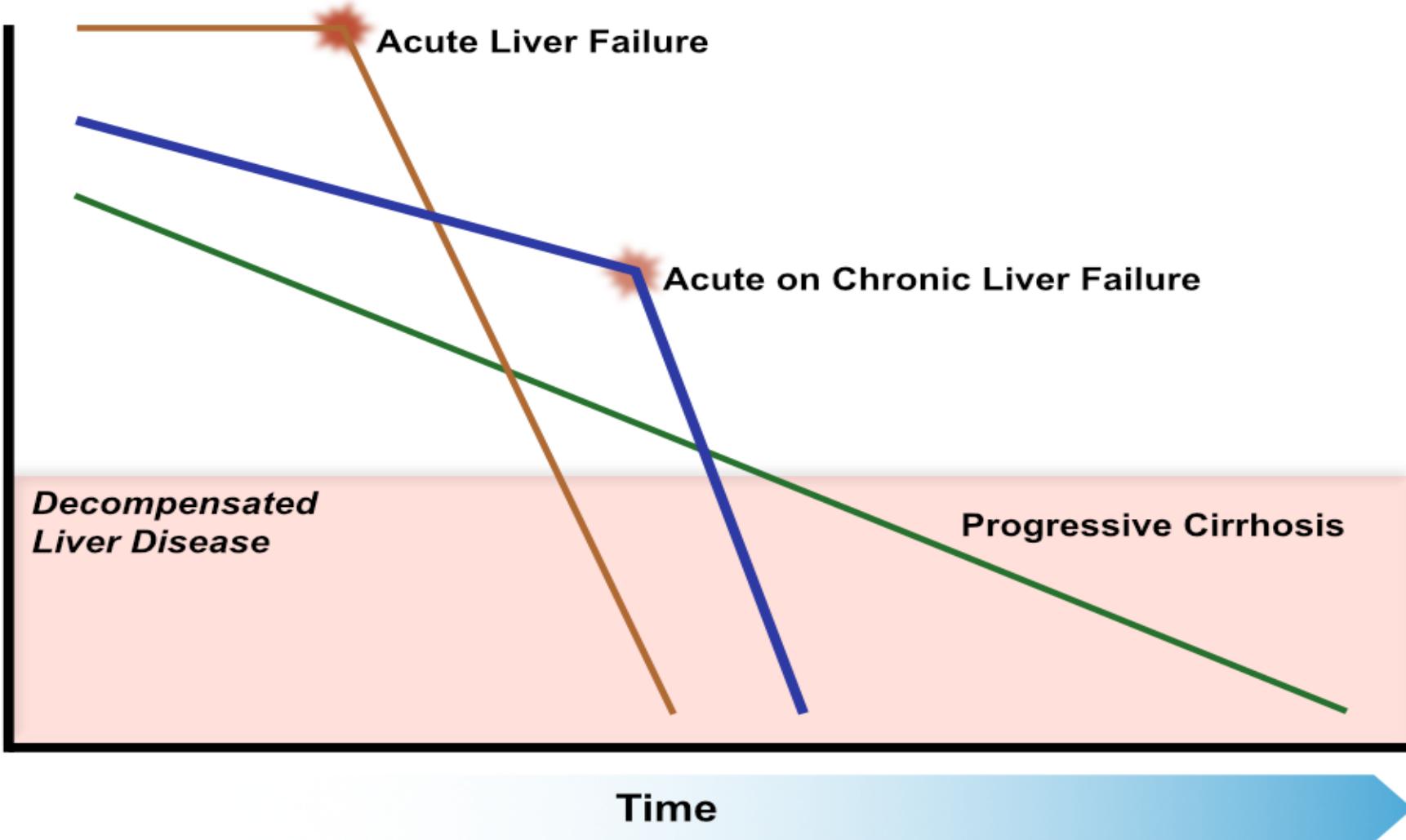
Speaker's bureau: Gilead, Abbvie, Intercept, Salix

What is acute-on-chronic liver failure (ACLF)?

“acute deterioration of preexisting chronic liver disease usually related to a precipitating event and associated with increased mortality at three months due to multisystem organ failure”

- Rajiv Jalan and Roger Williams. Blood Purification. 2002

Liver Function (%)



APASL

NACSELD

EASL-CLIF

-Definition developed based on expert consensus

-Acute jaundice & coagulopathy, followed by ascites \pm HE <4 weeks in patients with chronic liver disease, including but not requiring cirrhosis

-Excludes
a.Infection
b.Previously decompensated cirrhosis

-Derived from prospective study among patients with cirrhosis hospitalized with bacterial infection

-Organ failures include renal, brain, circulatory and respiratory failure based on need for therapeutic intervention (eg: dialysis, vasopressors, mechanical ventilation)

-Derived based on multi-center prospective study

-Pre-specified criteria using CLIF-OF criteria for: liver, renal, brain, respiratory, circulatory, and coagulation failure

APASL

NACSELD

EASL-CLIF

-Definition developed based on expert consensus

-Acute jaundice & coagulopathy, followed by ascites \pm HE <4 wks in patients with chronic liver disease, including but not requiring cirrhosis

-Excludes
a.Infection
b.Previously decompensated cirrhosis

-Derived from prospective study among patients with cirrhosis hospitalized with bacterial infection

-Organ failures include renal, brain, circulatory and respiratory failure based on need for therapeutic intervention (eg: dialysis, vasopressors, mechanical ventilation)

-Derived based on multi-center prospective study

-Pre-specified criteria using CLIF-OF criteria for: liver, renal, brain, respiratory, circulatory, and coagulation failure

CANONIC Study

- Multi-center, prospective cohort study in Europe of 1343 patients (96% did not receive LT)
- Pre-specified organ failure based on CLIF-SOFA score, validated in patients with cirrhosis
- ACLF grades defined based on association with organ failure and short-term mortality

Organ failures

Intrahepatic:

- Liver: bilirubin ≥ 12 mg/dL
- Coagulation: INR ≥ 2.5

Extrahepatic:

- Renal: creatinine ≥ 2.0 or HD
- Brain: grade 3-4 HE
- Circulatory: Need for vasopressors for hypotension
- Respiratory: $\text{PaO}_2/\text{FiO}_2 < 200$ or need for mechanical ventilation

28-day Mortality According to Organ Failure

No. and types of organ failures	All patients
No organ failure	39/874 (4.5)
One organ failure	39/267 (14.6)
Single liver failure	14/101 (13.9)
Single cerebral failure	3/30 (10.0)
Single coagulation failure	3/28 (10.7)
Single circulation or lung failure	3/22 (13.6)
Single kidney failure	16/86 (18.6)
Two organ failures	31/97 (32.0)
Three organ failures or more	33/42 (78.6)

ACLF Grading System

ACLF 1

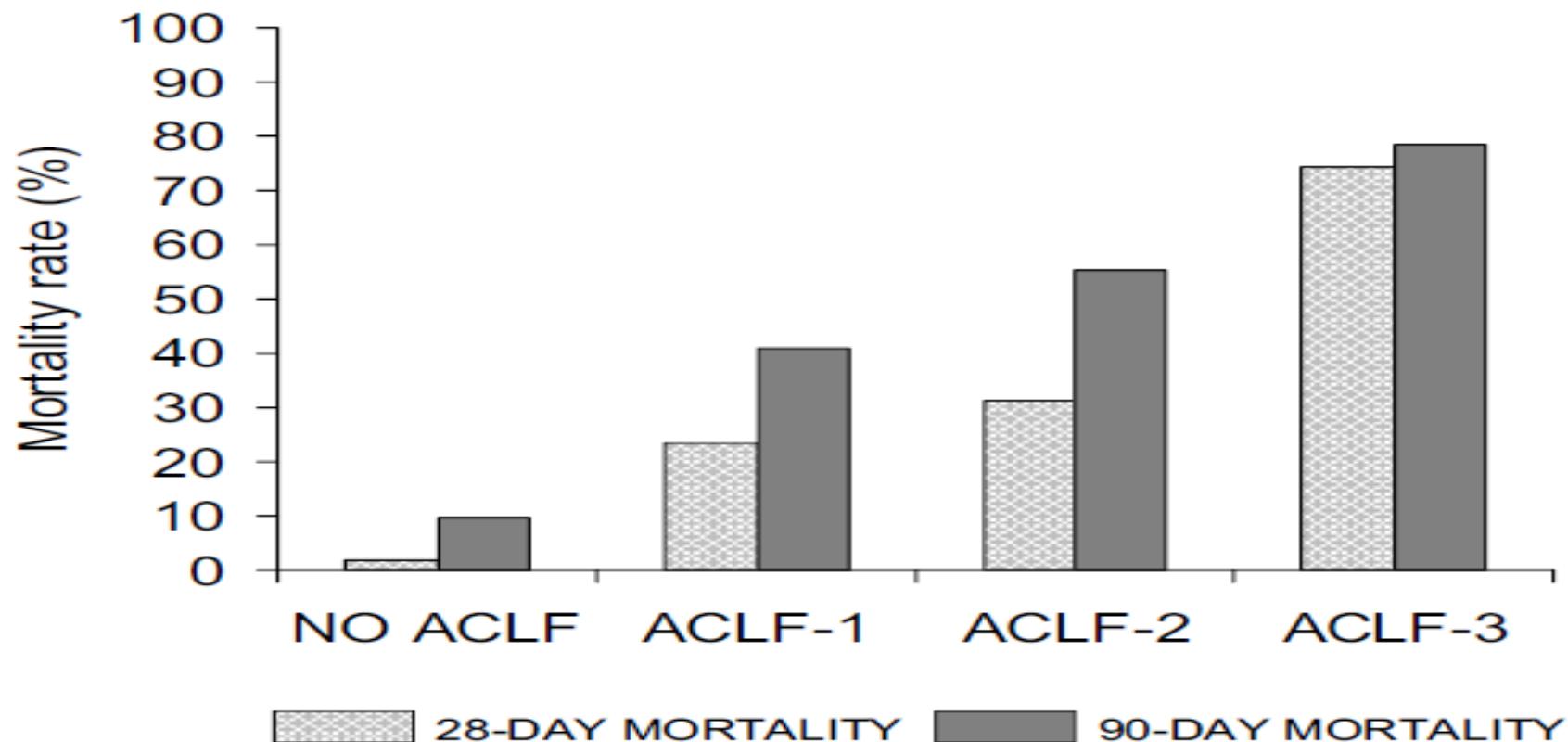
- Patients with renal failure (creatinine ≥ 2.0 or HD)
- Patients with single non-renal organ failure with:
 - Serum creatinine ≥ 1.5 and < 2 mg/dl
 - OR
 - Hepatic encephalopathy grade 1-2

ACLF 2

- Patients with 2 organ failures

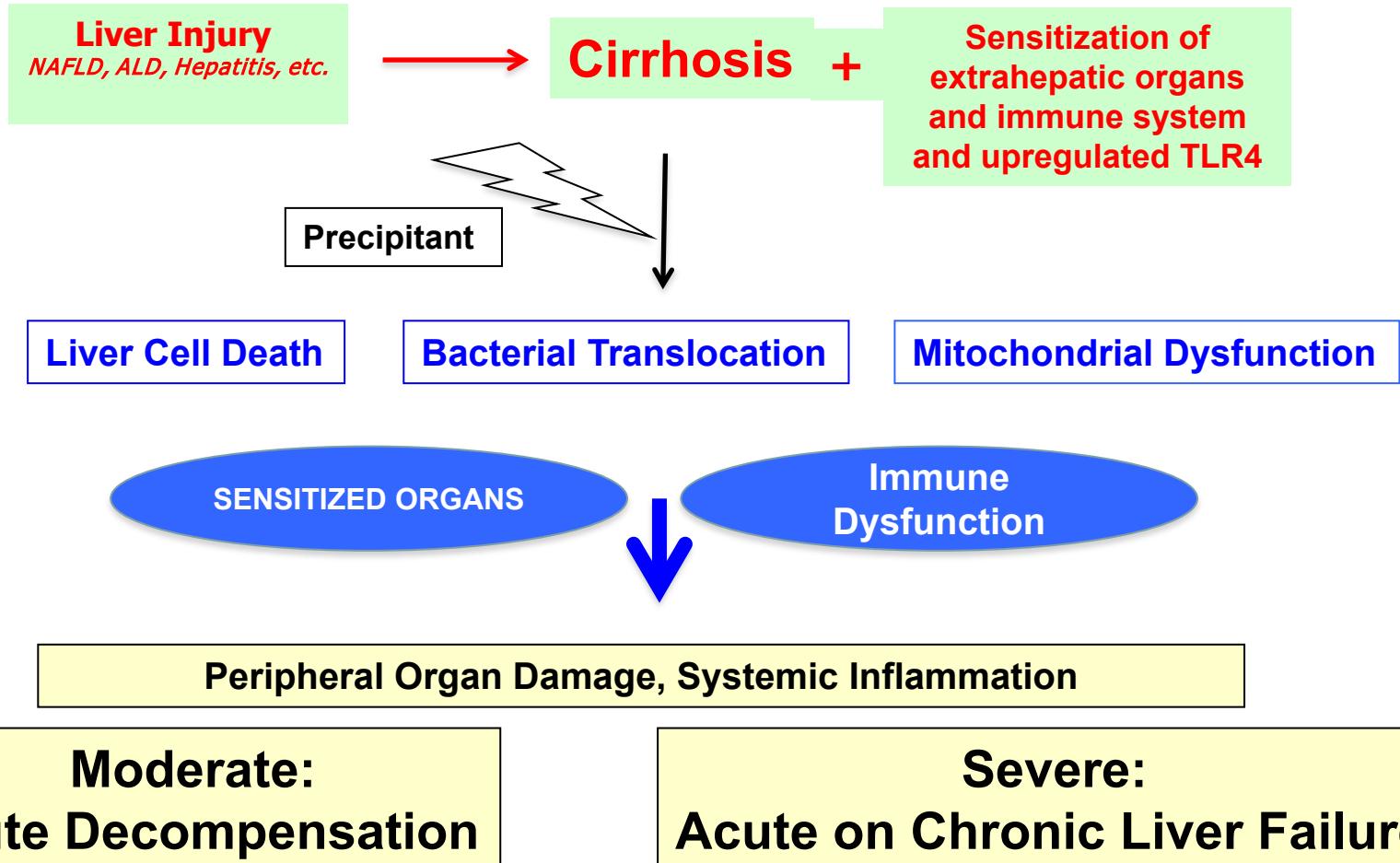
ACLF 3

- Patients with 3 or more organ failures



Supplementary Figure 2. Mortality rate at 28 days and 90 days according to the grade of ACLF.

Decompensated Cirrhosis vs ACLF



Renin and Inflammatory Cytokines

	Healthy controls N=40	Decompensated cirrhosis N=285	ACLF N=237	p-value*
<i>Renin-angiotensin System</i>				
PRC (u IU/ml)	8 (6-17)	65 (17-242)	134 (36-378)	<0.001
Cytokines				
TNF α (pg/ml)	9 (7-12)	20 (14-27)	29 (17-41)	<0.001
IL-6 (pg/ml)	0.3 (0.3-0.3)	21 (11-41)	39 (17-115)	<0.001
IL-8 (pg/ml)	1.6 (0.6-3.3)	37 (20-76)	84 (41-169)	<0.001
IL-10 (pg/ml)	1.1 (0.4-1.1)	3.4 (1.1-9.2)	8.1 (2.1-29.9)	<0.001
IL-1ra (pg/ml)	7 (3-9)	10 (5-22)	23 (9-63)	<0.001

Renin and Inflammatory Cytokines

	Healthy controls N=40	Decompensated cirrhosis N=285	ACLF N=237	p-value*
Renin-angiotensin System				
PRC (u IU/ml)	8 (6-17)	65 (17-242)	134 (36-378)	<0.001
Cytokines				
TNF α (pg/ml)	9 (7-12)	20 (14-27)	29 (17-41)	<0.001
IL-6 (pg/ml)	0.3 (0.3-0.3)	21 (11-41)	39 (17-115)	<0.001
IL-8 (pg/ml)	1.6 (0.6-3.3)	37 (20-76)	84 (41-169)	<0.001
IL-10 (pg/ml)	1.1 (0.4-1.1)	3.4 (1.1-9.2)	8.1 (2.1-29.9)	<0.001
IL-1ra (pg/ml)	7 (3-9)	10 (5-22)	23 (9-63)	<0.001

Renin and Inflammatory Cytokines

	Healthy controls N=40	Decompensated cirrhosis N=285	ACLF N=237	p-value*
Renin-angiotensin System				
PRC (u IU/ml)	8 (6-17)	65 (17-242)	134 (36-378)	<0.001
Cytokines				
TNF α (pg/ml)	9 (7-12)	20 (14-27)	29 (17-41)	<0.001
IL-6 (pg/ml)	0.3 (0.3-0.3)	21 (11-41)	39 (17-115)	<0.001
IL-8 (pg/ml)	1.6 (0.6-3.3)	37 (20-76)	84 (41-169)	<0.001
IL-10 (pg/ml)	1.1 (0.4-1.1)	3.4 (1.1-9.2)	8.1 (2.1-29.9)	<0.001
IL-1ra (pg/ml)	7 (3-9)	10 (5-22)	23 (9-63)	<0.001

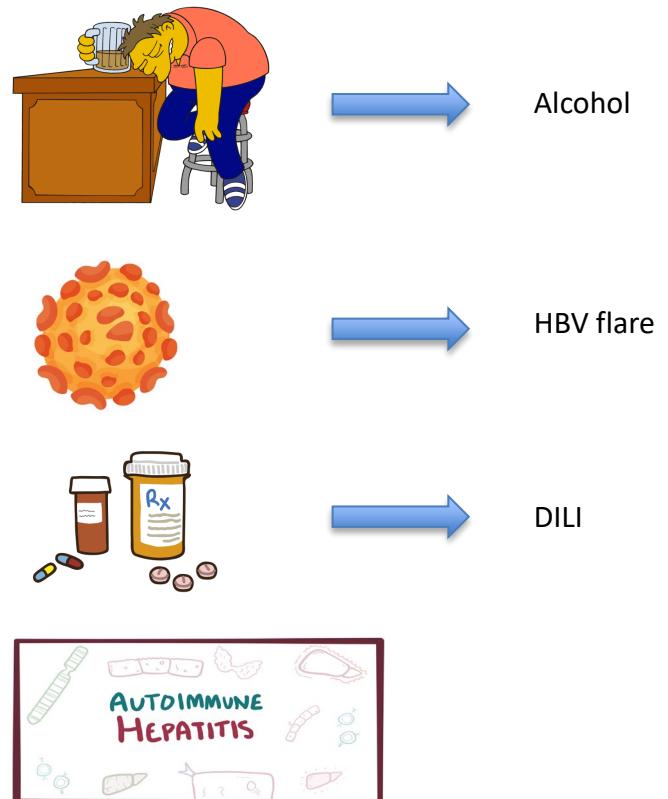
Cytokines and ACLF grade

	ACLF-1 N=126	ACLF-2 N=86	ACLF-3 N=25	p-value*
<i>Renin-angiotensin system</i>				
<i>PRC (u IU/ml)</i>	169 (40-383)	114 (28-352)	87 (33-258)	0.771
<i>Cytokines</i>				
<i>TNFα (pg/ml)</i>	30 (21-43)	26 (15-36)	32 (17-43)	0.029
<i>IL-6 (pg/ml)</i>	34 (18-96)	43 (13-106)	111 (32-355)	0.018
<i>IL-8 (pg/ml)</i>	62 (37-112)	97 (48-192)	144 (80-292)	<0.001
<i>IL-10 (pg/ml)</i>	4.3 (1.1-17.9)	15.3 (5.5-41.5)	12.4 (6.6-40.8)	<0.001
<i>IL-1ra (pg/ml)</i>	17 (10-45)	26 (8-63)	49 (24-135)	0.019

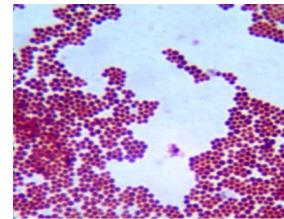
Cytokines and ACLF grade

	ACLF-1 N=126	ACLF-2 N=86	ACLF-3 N=25	p-value*
<i>Renin-angiotensin system</i>				
PRC (u IU/ml)	169 (40-383)	114 (28-352)	87 (33-258)	0.771
<i>Cytokines</i>				
TNF α (pg/ml)	30 (21-43)	26 (15-36)	32 (17-43)	0.029
IL-6 (pg/ml)	34 (18-96)	43 (13-106)	111 (32-355)	0.018
IL-8 (pg/ml)	62 (37-112)	97 (48-192)	144 (80-292)	<0.001
IL-10 (pg/ml)	4.3 (1.1-17.9)	15.3 (5.5-41.5)	12.4 (6.6-40.8)	<0.001
IL-1ra (pg/ml)	17 (10-45)	26 (8-63)	49 (24-135)	0.019

Precipitants of ACLF (Intrahepatic)



Precipitants of ACLF (Extrahepatic)



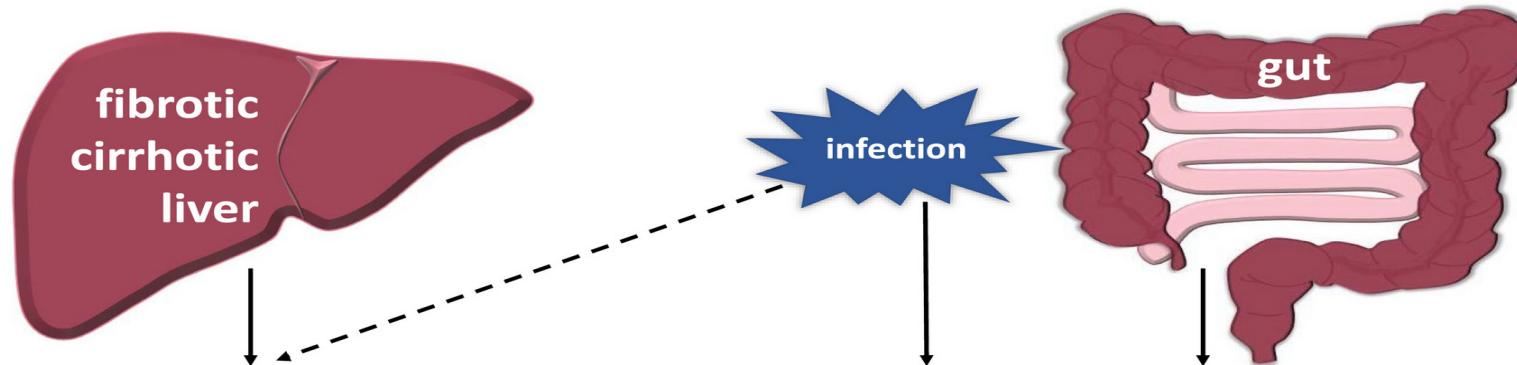
→ Bacterial infection



→ Gastrointestinal bleed



→ Surgery



Damage-Associated Molecular Patterns: DAMPs

HMGB1, mitochondrial DNA, ATP, uric acid

Pathogen-Associated Molecular Patterns: PAMPs

LPS, peptidoglycan, bacterial DNA, fungal components

Host innate immune activation – Pattern recognition receptor

TLRs



NLRs



MyD88, IRAK, NF κ B



Inflammatory cytokines, chemokines

Inflammasome activation



IL-1 α , IL-18, IL-33

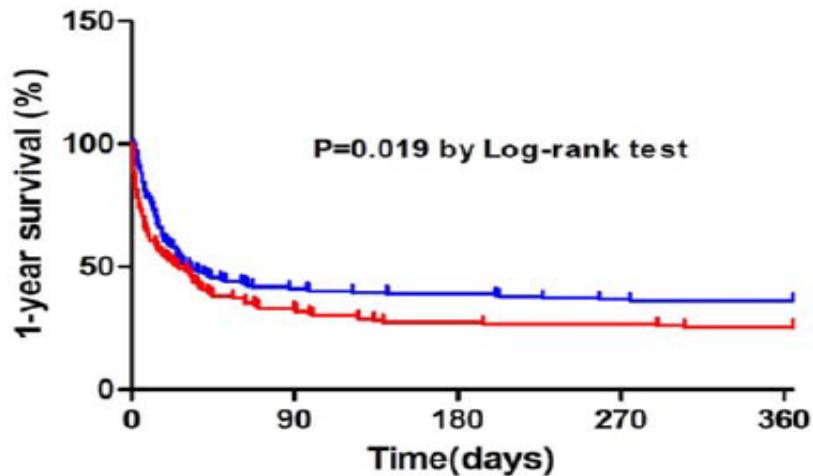
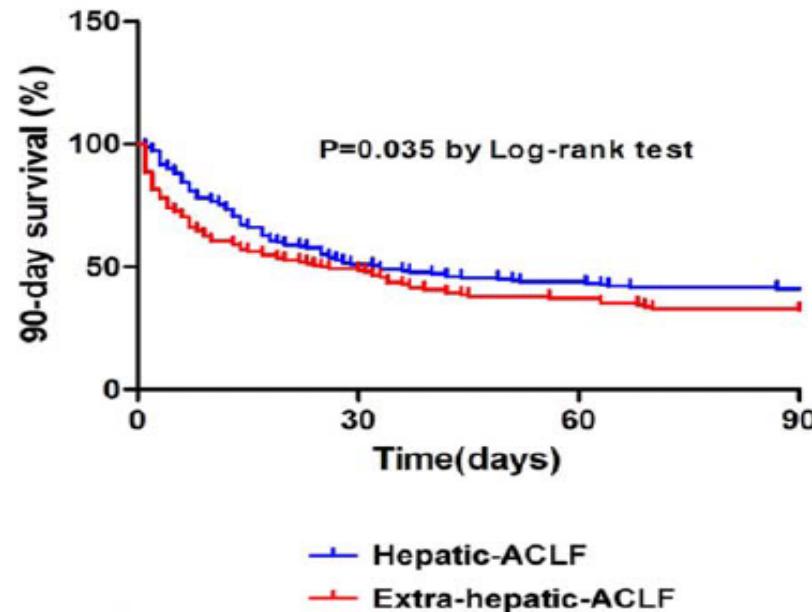
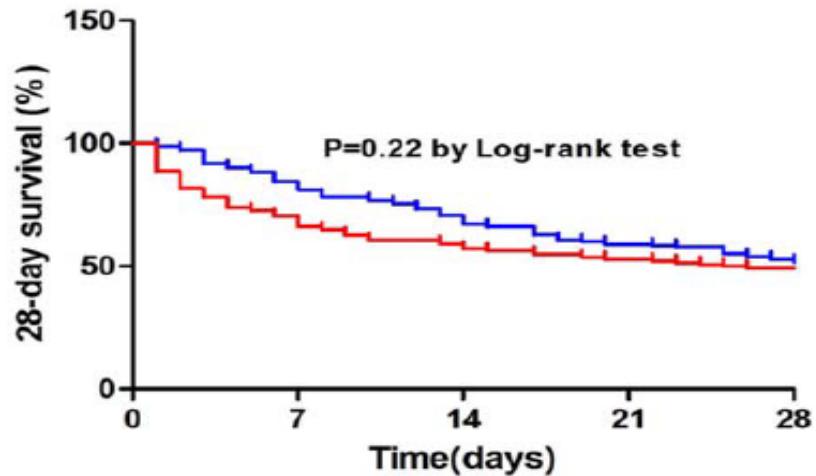
Sepsis

SIRS

Organ Failure: Liver, Kidney, Lung, Brain, Heart

Organ Failure n (%)	Intrahepatic precipitant (N=180)	Extrahepatic precipitant (n=142)
Liver	171 (95.0) 	75 (52.8)
Kidney	9 (5.0)	57 (40.1)
Brain	15 (8.3)	27 (19.0)
Coagulation	155 (86.1) 	74 (52.1)
Lung	5 (2.8)	26 (18.3)
Circulatory	4 (2.2)	32 (22.5)

Organ Failure n (%)	Intrahepatic precipitant (N=180)	Extrahepatic precipitant (n=142)
Liver	171 (95.0)	75 (52.8)
Kidney	9 (5.0)	57 (40.1)
Brain	15 (8.3)	27 (19.0)
Coagulation	155 (86.1)	74 (52.1)
Lung	5 (2.8)	26 (18.3)
Circulatory	4 (2.2)	32 (22.5)



Role of Liver Transplantation

- Waitlist mortality
- Short-term survival outcomes after transplantation
- Futility of transplantation
- Optimizing post-transplant survival
- Outcomes beyond short-term post-transplant survival

Patient Case (KN)

- In year 2013, 28-year-old female with cirrhosis from autoimmune hepatitis
 - Social history: mother of 7-year-old son, job “love him and make him happy”
- Listed for LT with stable decompensated cirrhosis (HE, edema) and baseline MELD score of 17, blood type O
- Admitted for variceal bleed, develops HRS needing dialysis
- MELD score rises to 36 (INR=1.9, Tbili=12).
- Day 6, transferred to ICU for pressors → ACLF-3 (MELD score 36)

Patient Case (KN)

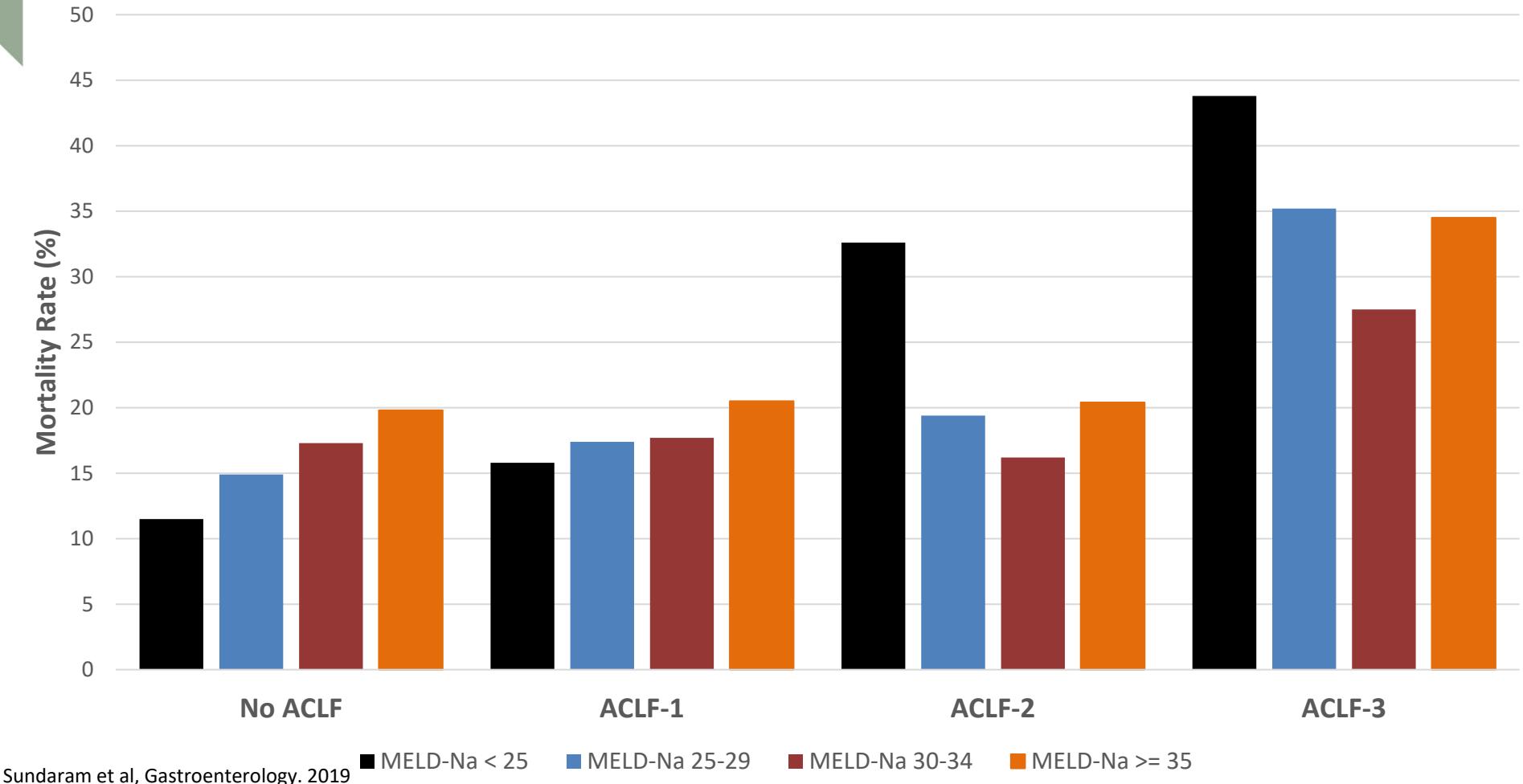
- Day 11, top of list (MELD=40) BUT another patient (CW) admitted with ALF
- Day 12, patient CW transplanted
- Day 16, patient's MELD=40, requiring 2-3 mcg levophed, waxing/waning mental status, not ventilated and I get the following text from our junior surgeon:

“Guess what. I got a primary offer for her. Going on procurement soon”
- Later that day I get this text:

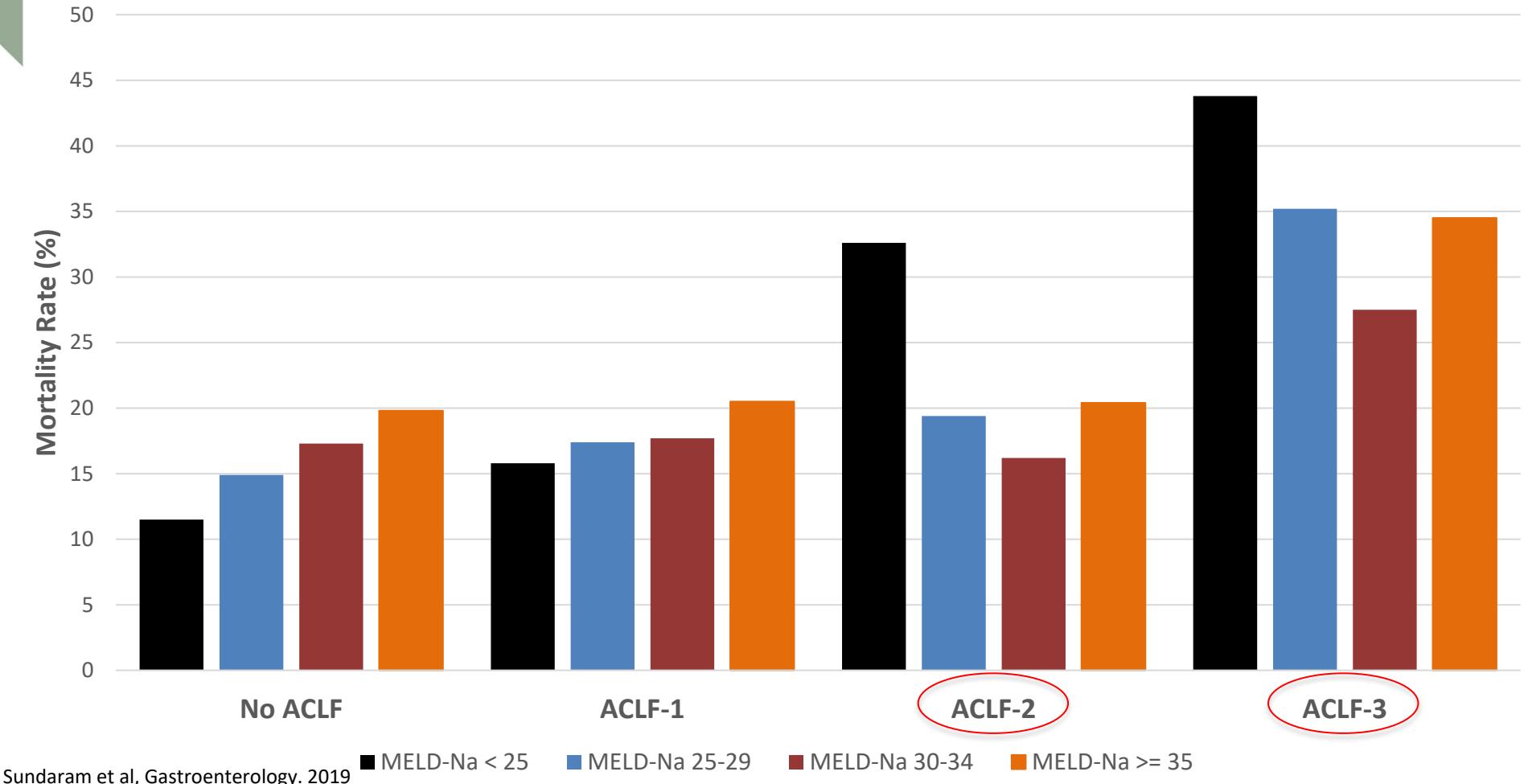
“Liver looks good but donor is 75 years old and we think she can wait”

Waitlist mortality and organ allocation policy

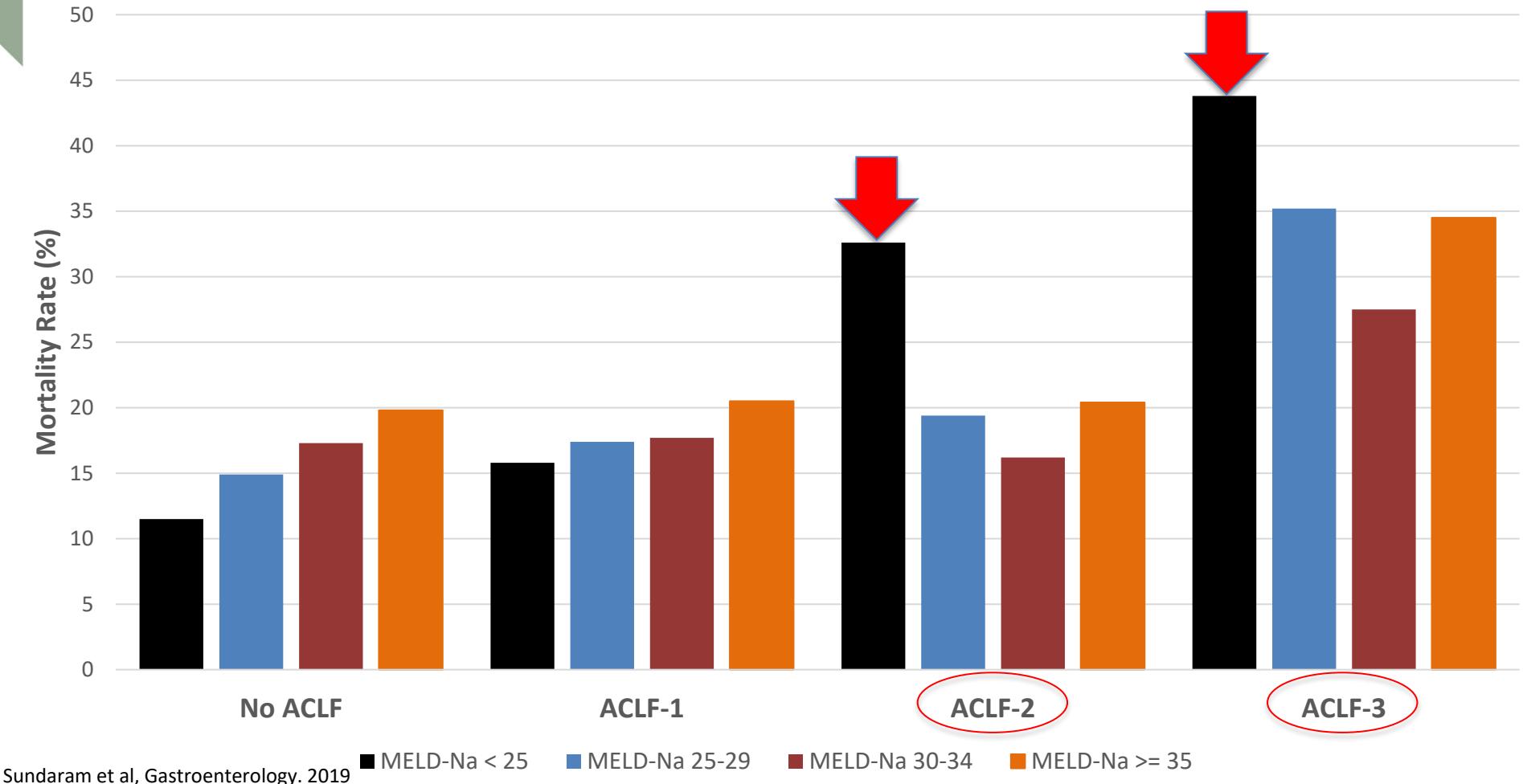
Death or Waitlist Removal Within 28 Days



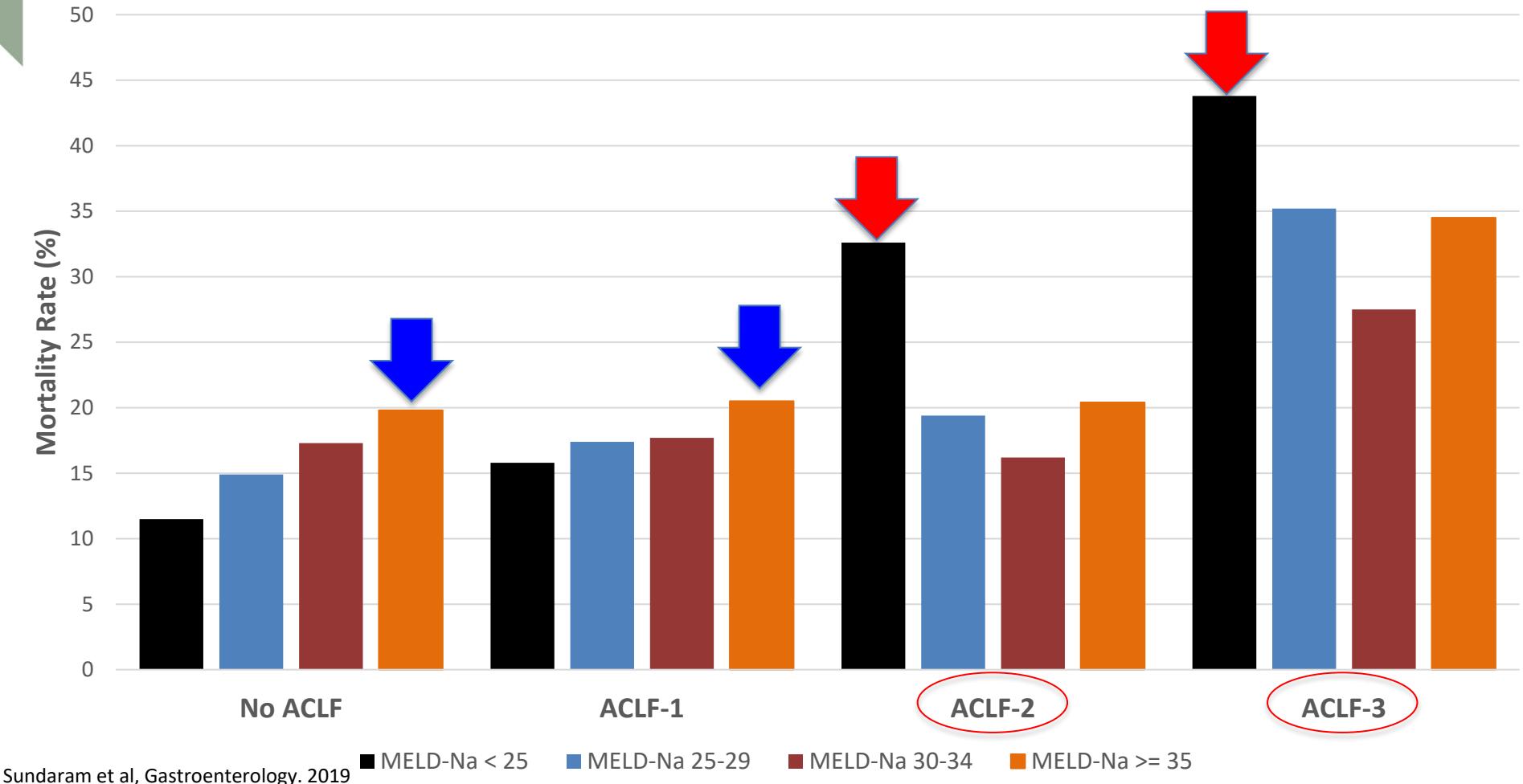
Death or Waitlist Removal Within 28 Days



Death or Waitlist Removal Within 28 Days

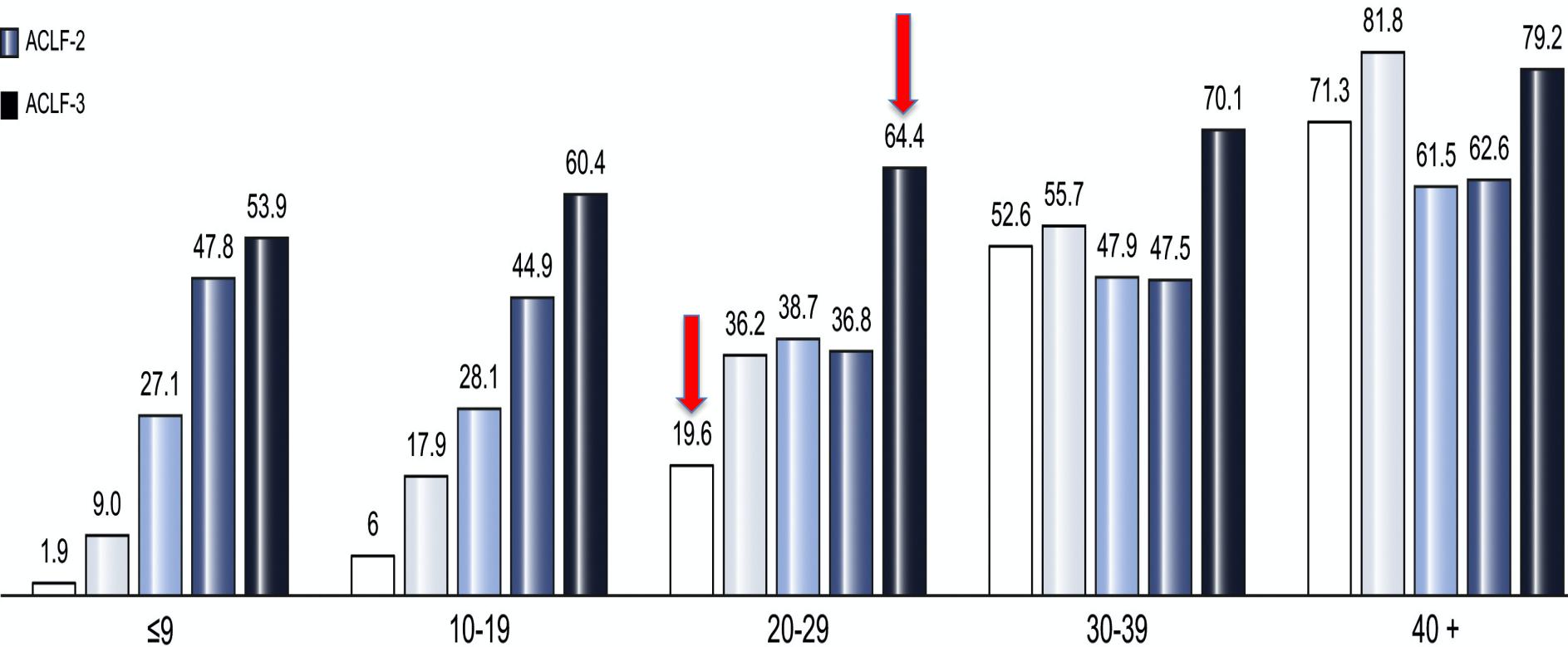


Death or Waitlist Removal Within 28 Days

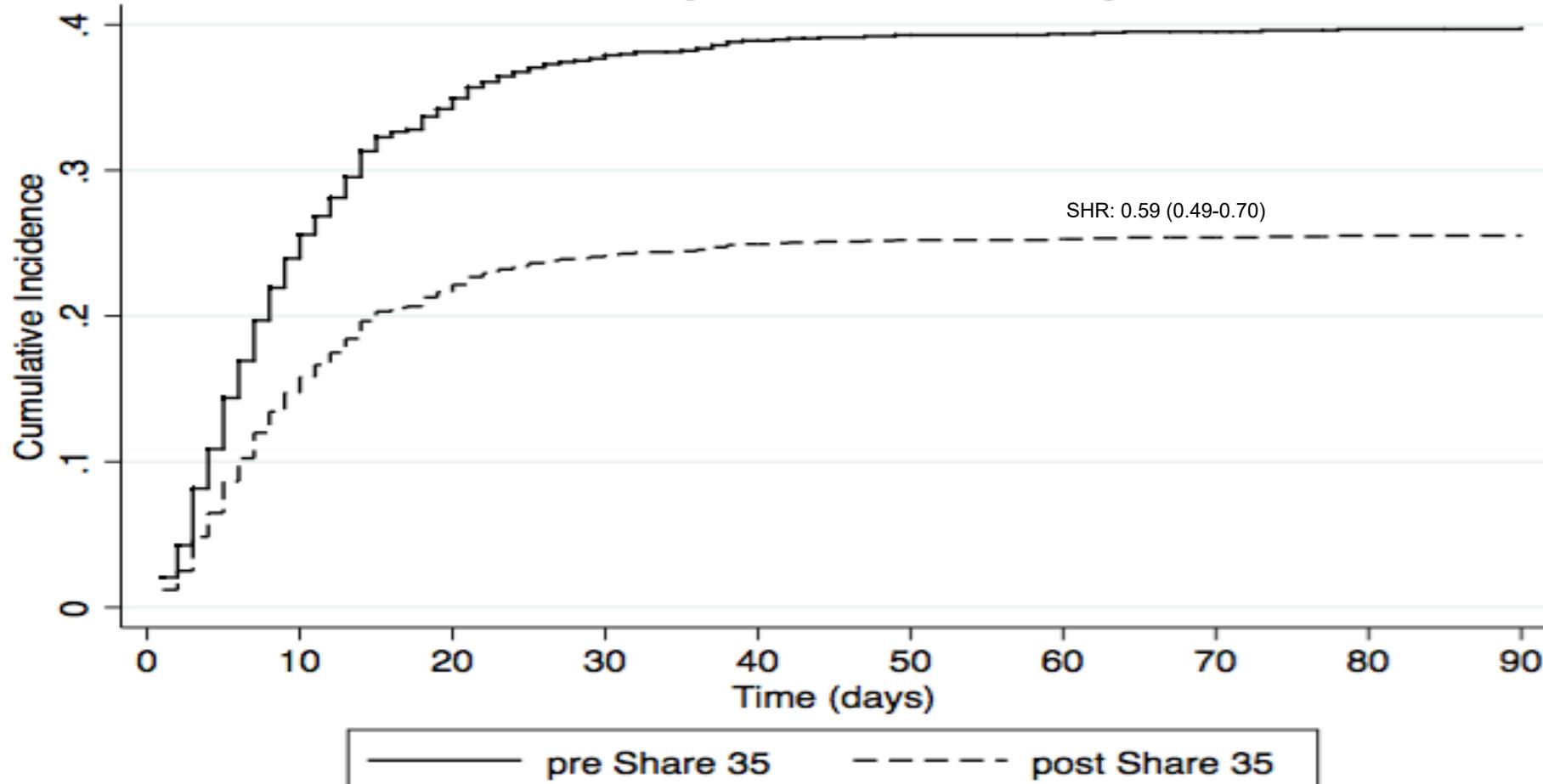


90-day mortality (%)

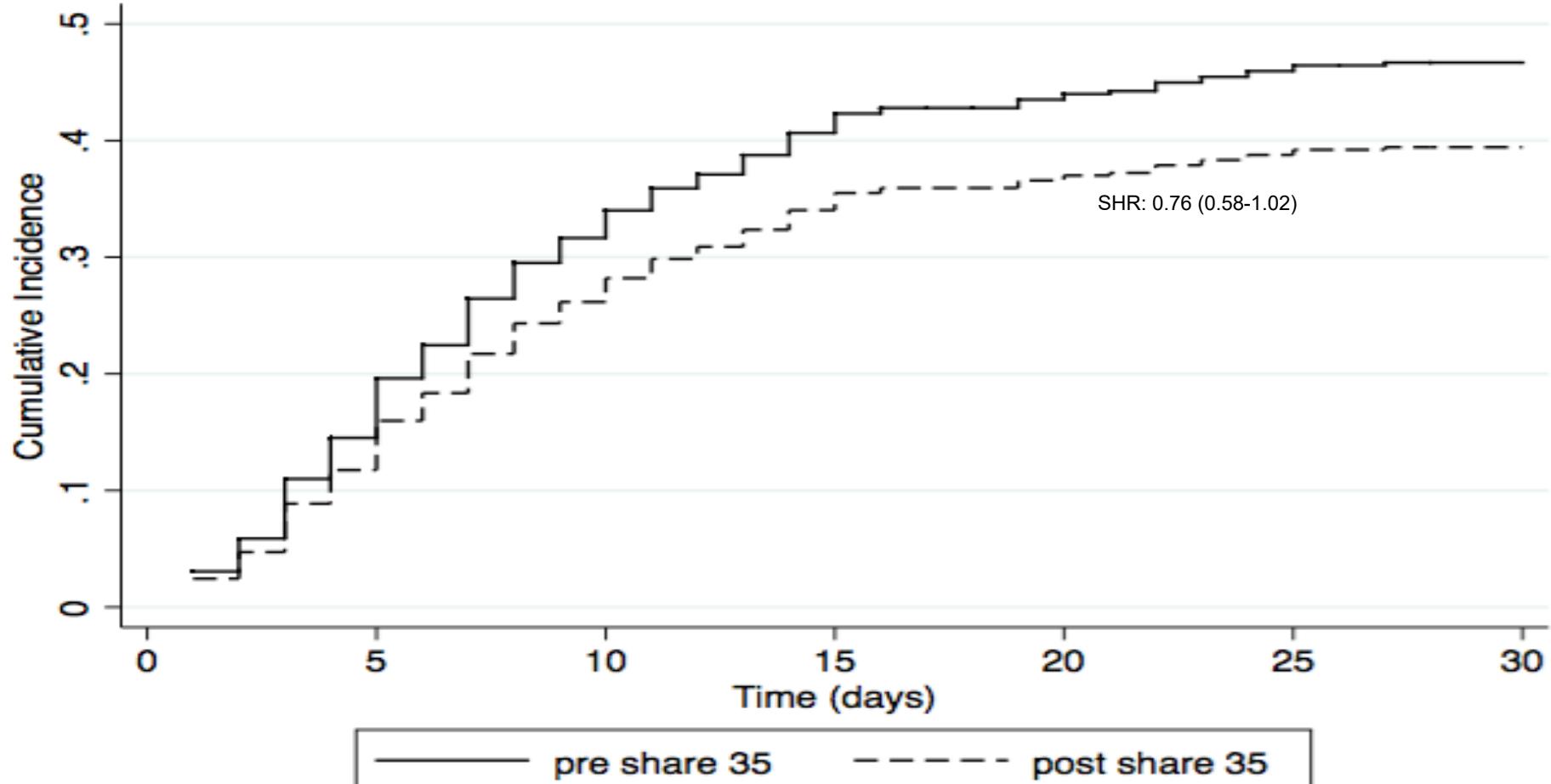
- Expected
- non ACLF
- ACLF-1
- ACLF-2
- ACLF-3



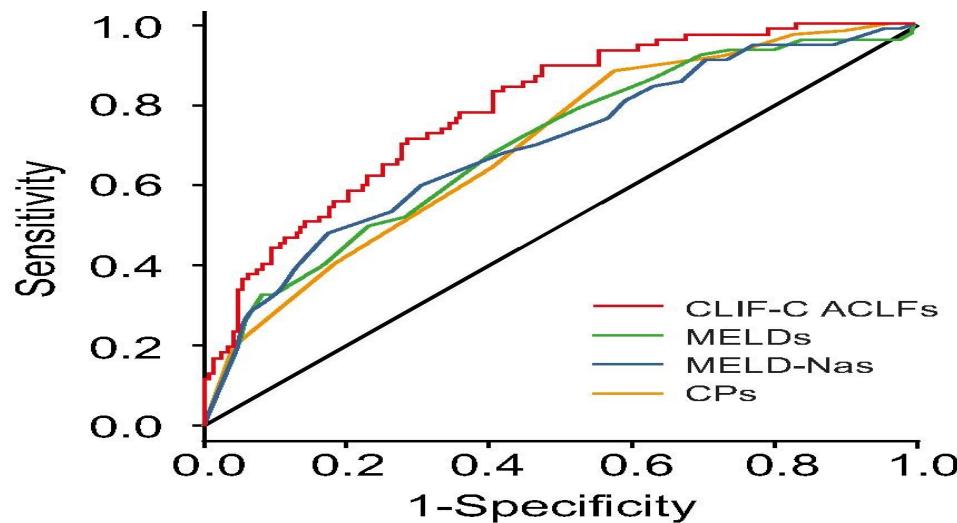
90-day waitlist mortality



28-day waitlist mortality

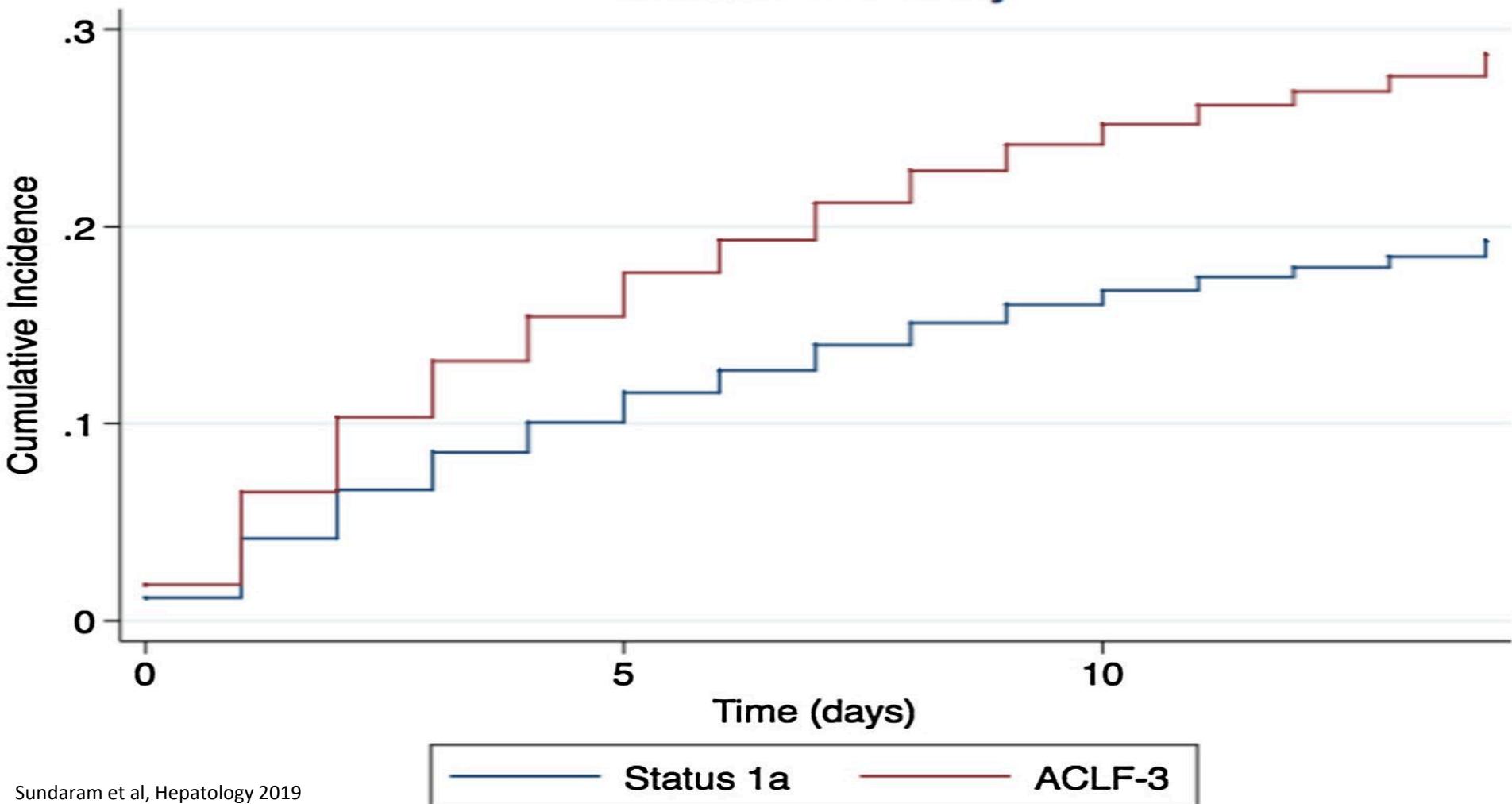


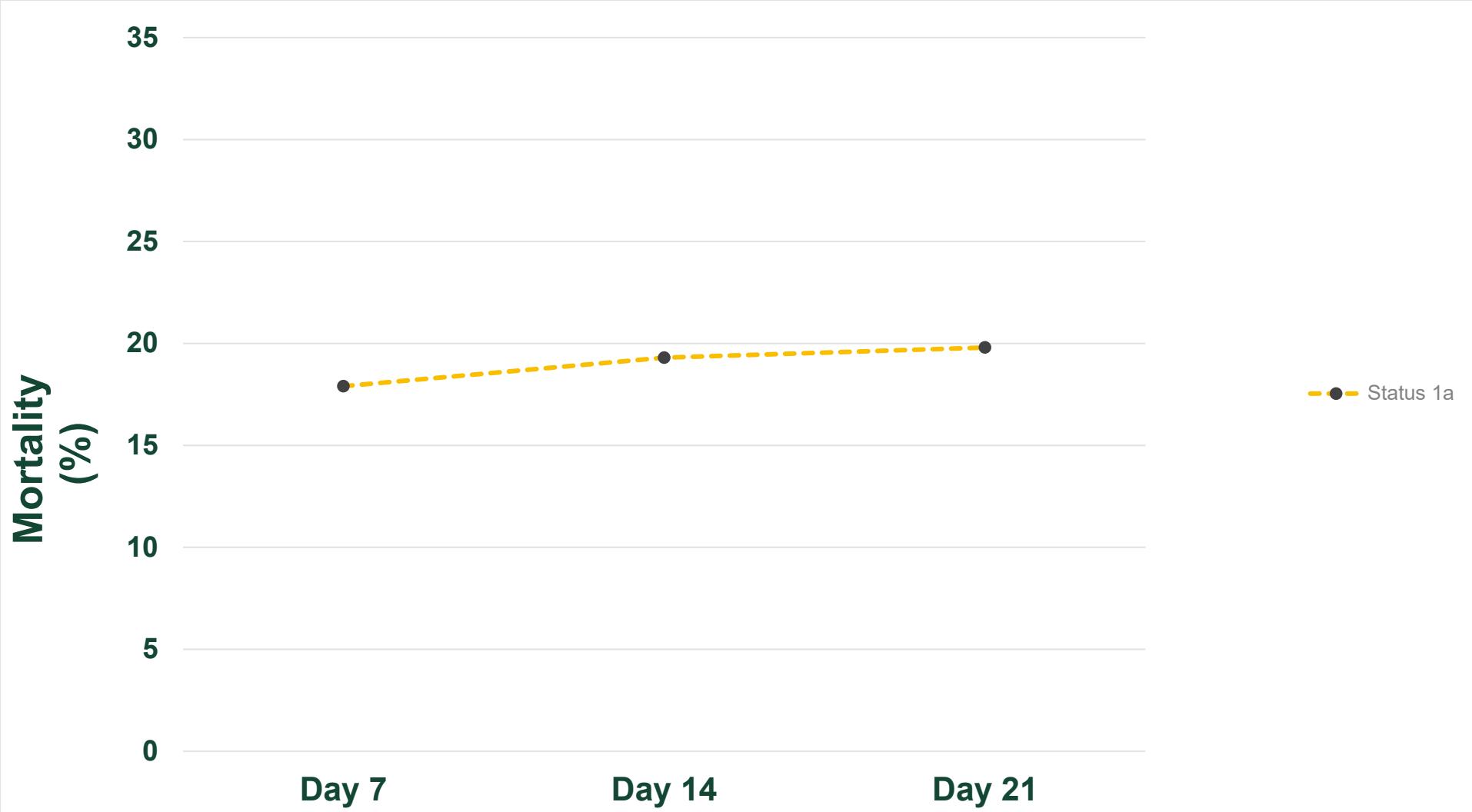
CLIF-C ACLF Score

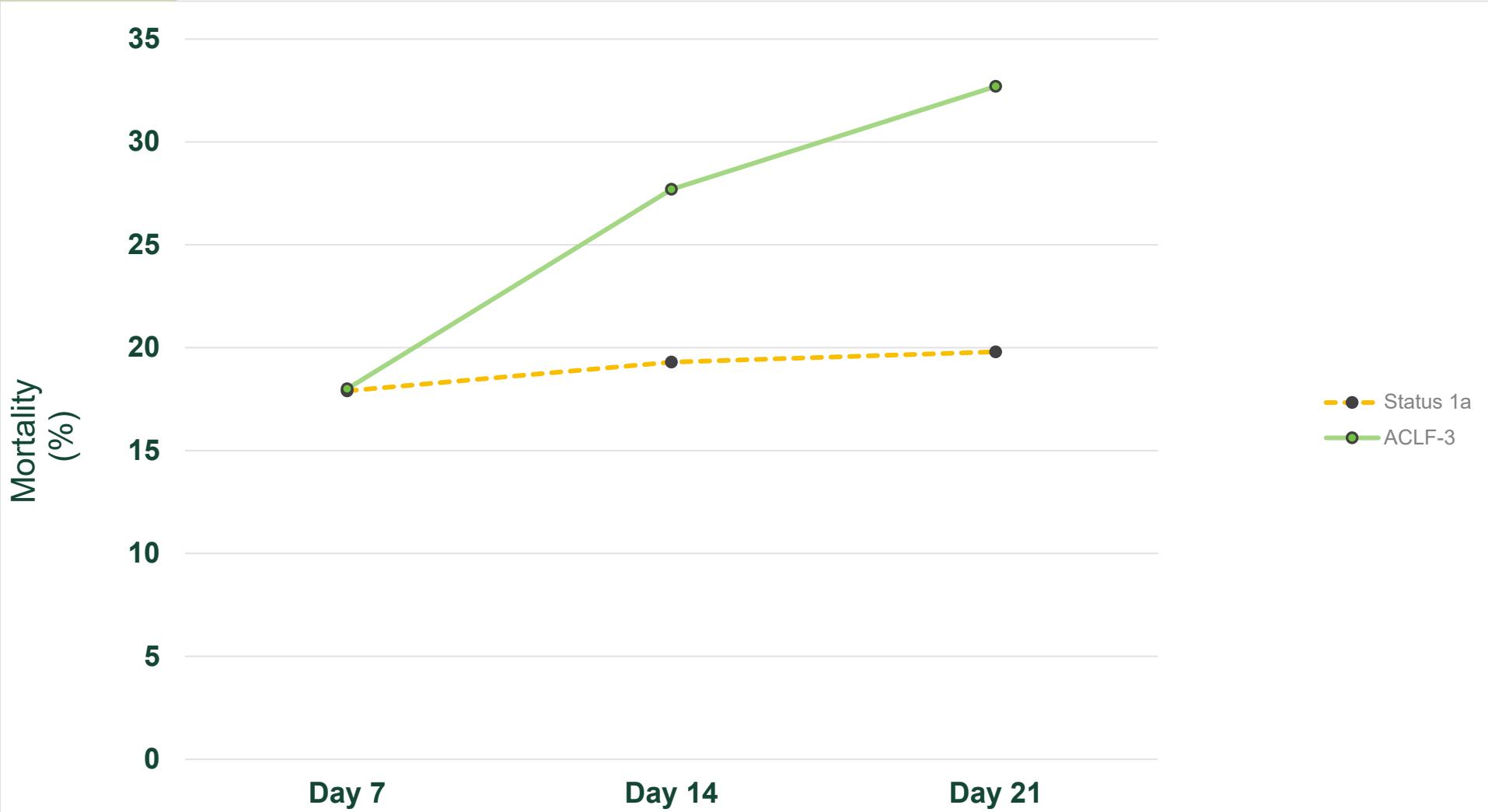


	AUROC (95% CI)	<i>p</i> value vs. CLIF-C ACLF
CLIF-C ACLFs	0.79 (0.73-0.85)	
MELDs	0.70 (0.62-0.77)	0.0089
MELD-Nas	0.70 (0.62-0.77)	0.0097
CPs	0.70 (0.63-0.77)	0.0075

Waitlist mortality





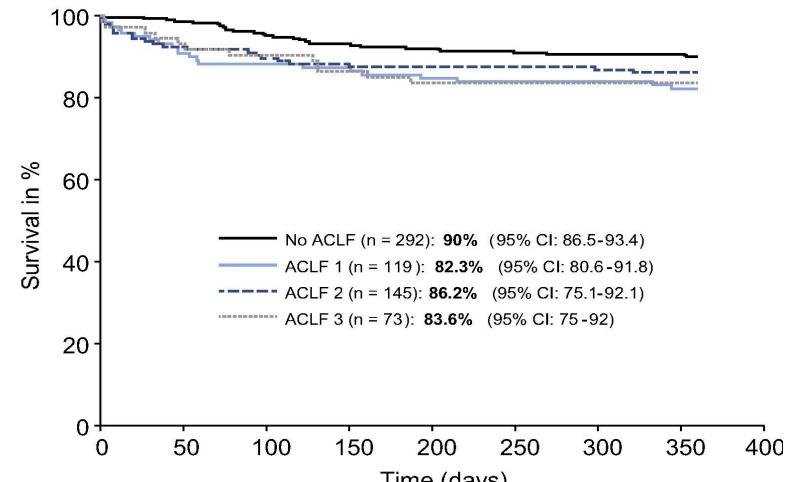


	Univariable model	Model 1	Model 2
Status 1a	Reference	Reference	Reference
ACLF-3	1.67 (1.53-1.83)	1.45 (1.31-1.61)	
MELD-Na < 36	Reference	Reference	1.30 (1.16-1.47)
MELD-Na 36-40	1.06 (0.96-1.17)	1.16 (1.04-1.29)	1.38 (1.22-1.56)
MELD-Na >40	1.49 (1.36-1.64)	1.51 (1.37-1.67)	1.77 (1.59-1.97)

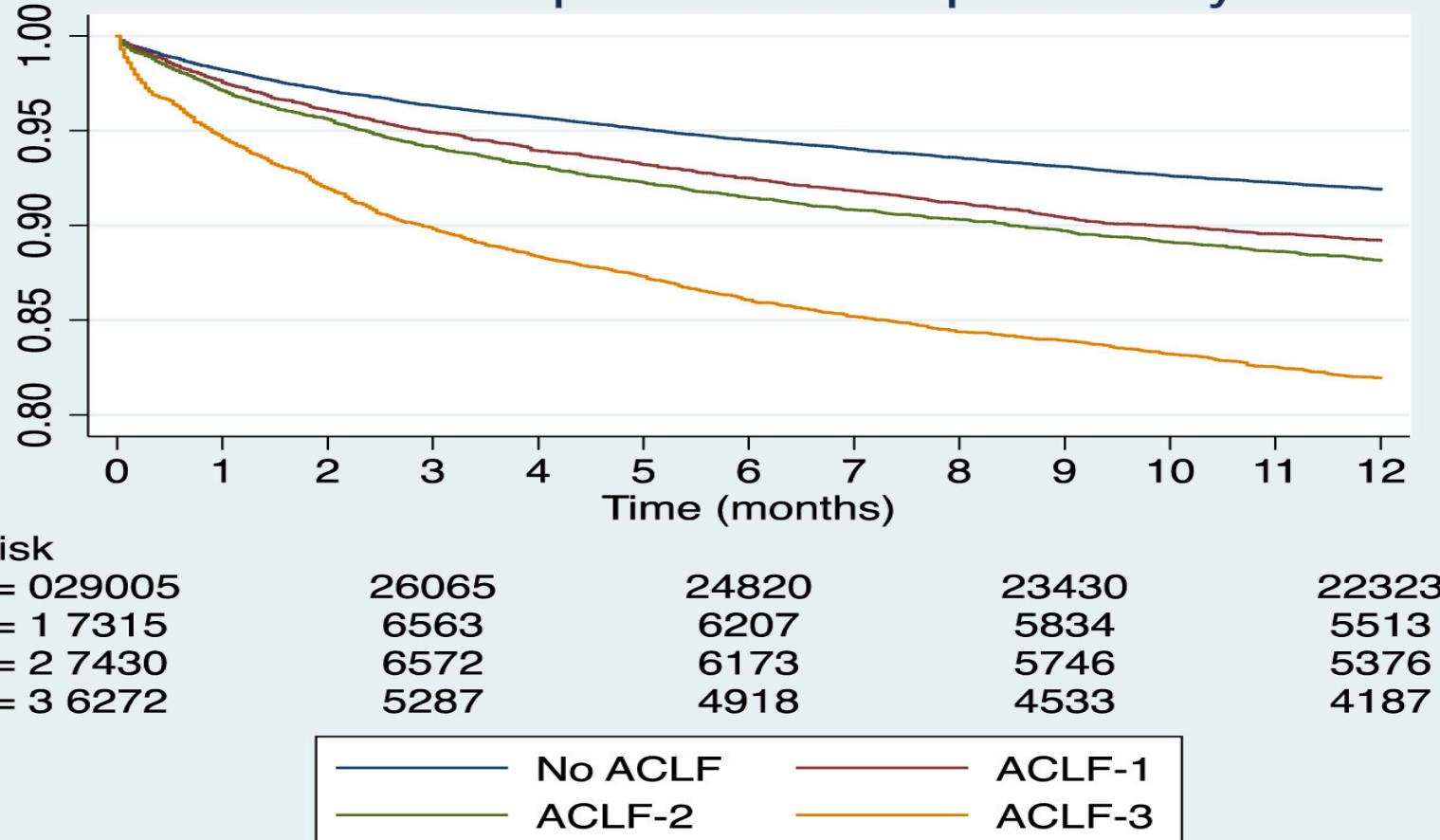
Survival outcomes after transplantation

Multicenter data - Europe

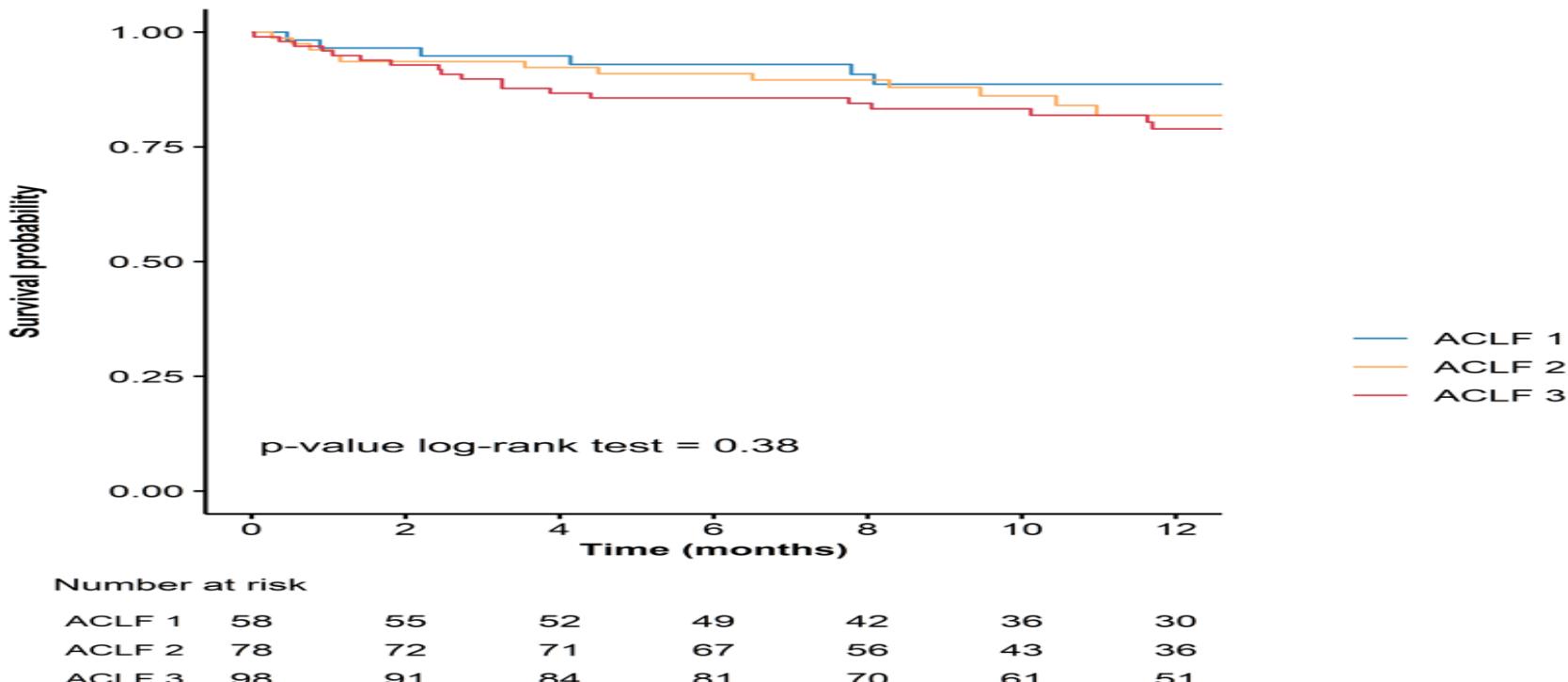
- Patients excluded from LT:
 - Active bleeding
 - Sepsis controlled < 24h
 - Noradrenaline > 3mg/h
 - Severe ARDS



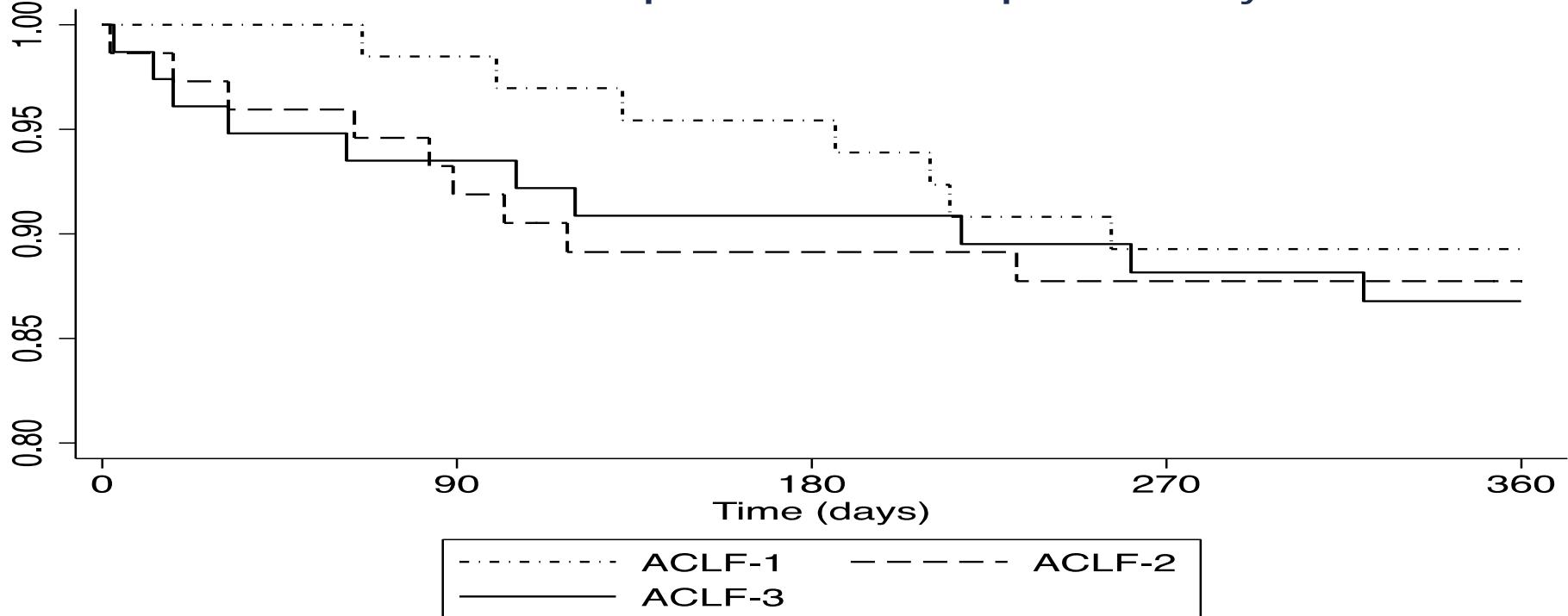
Post-transplant survival probability



Post-transplant survival probability



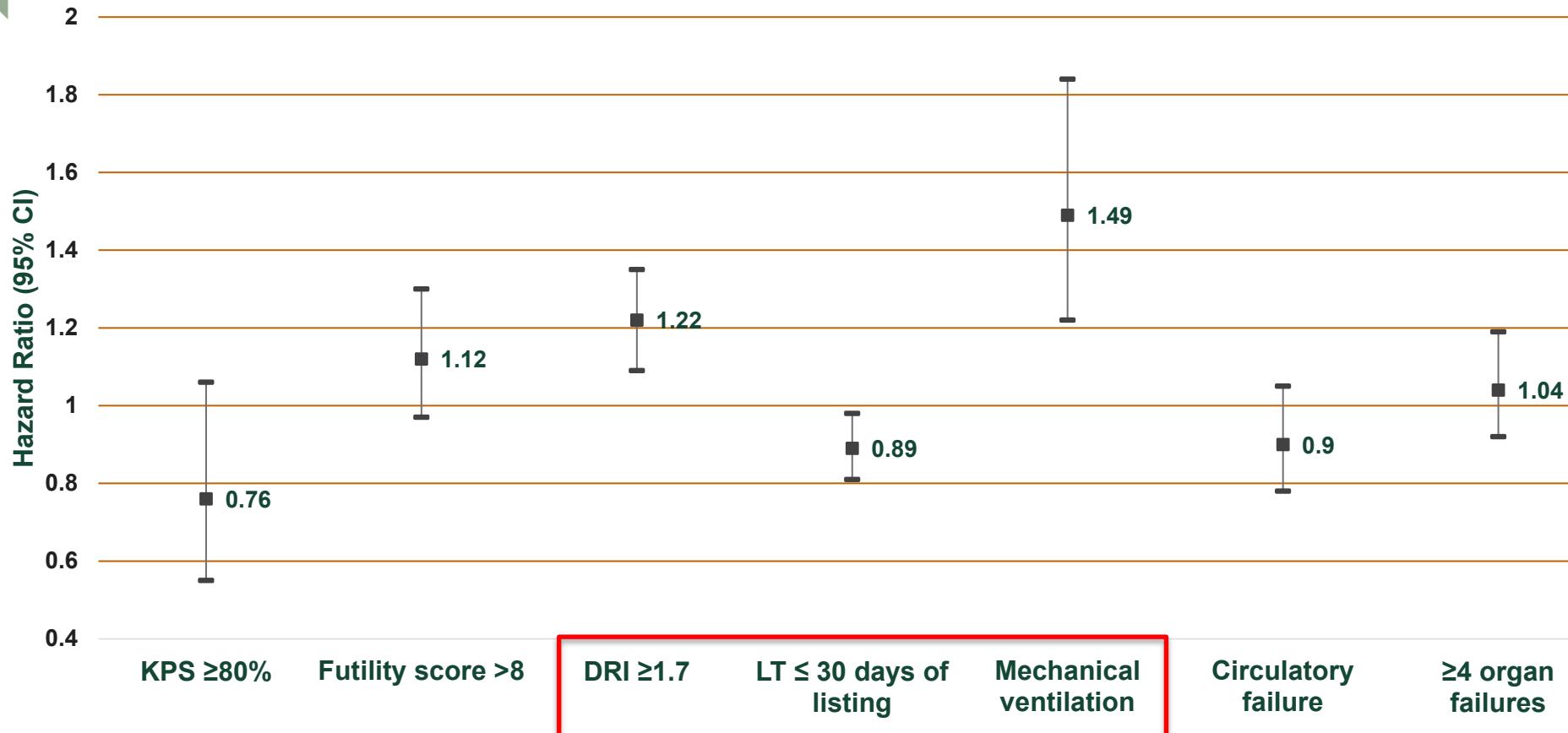
Post-transplant survival probability



	30 days	90 days	180 days	365 days
ACLF-1	1.00 N=61	0.985 (0.897-0.998) N=60	0.951 (0.865-0.985) N=58	0.885 (0.788-0.947) N=54
ACLF-2	0.986 (0.896-0.993) N=73	0.932 (0.828-0.963) N=69	0.919 (0.828-0.963) N=68	0.878 (0.777-0.934) N=65
ACLF-3	0.974 (0.884-0.987) N=75	0.948 (0.851-0.972) N=73	0.909 (0.818-0.955) N=70	0.857 (0.768-0.927) N=66

Futility of transplantation

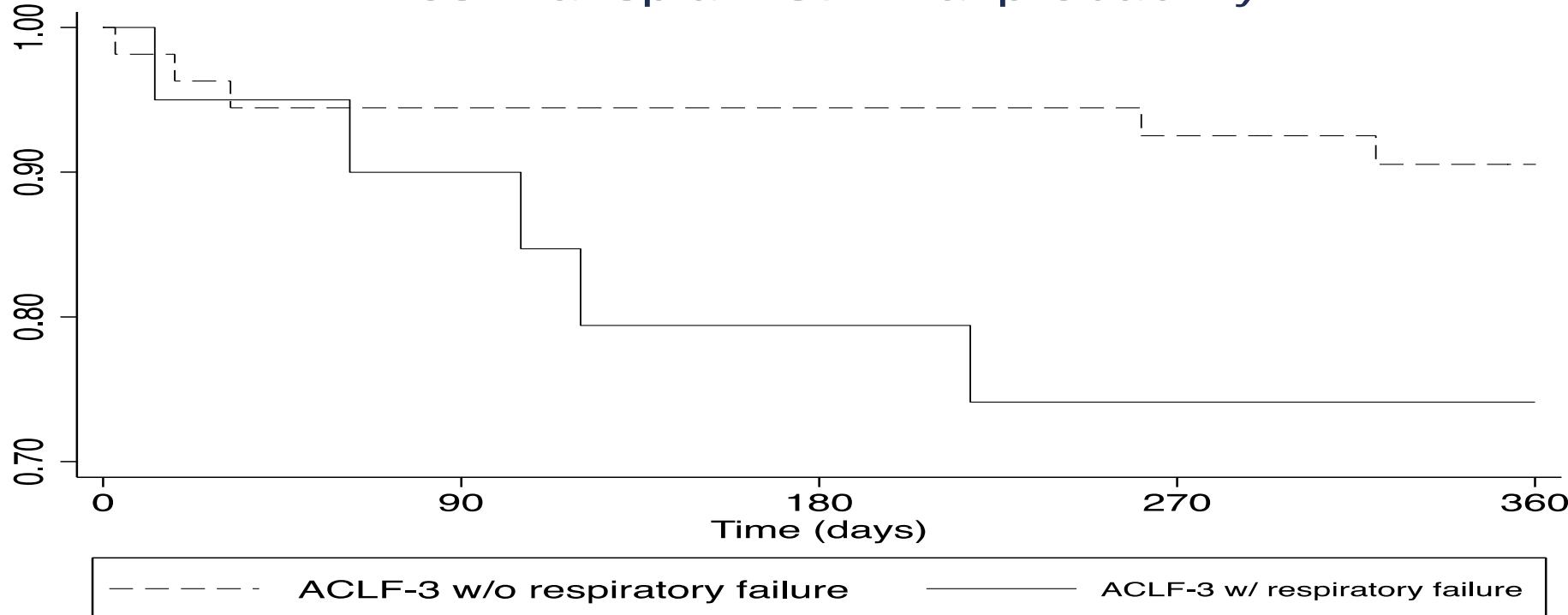
Risk factors for 1-year post-transplant mortality



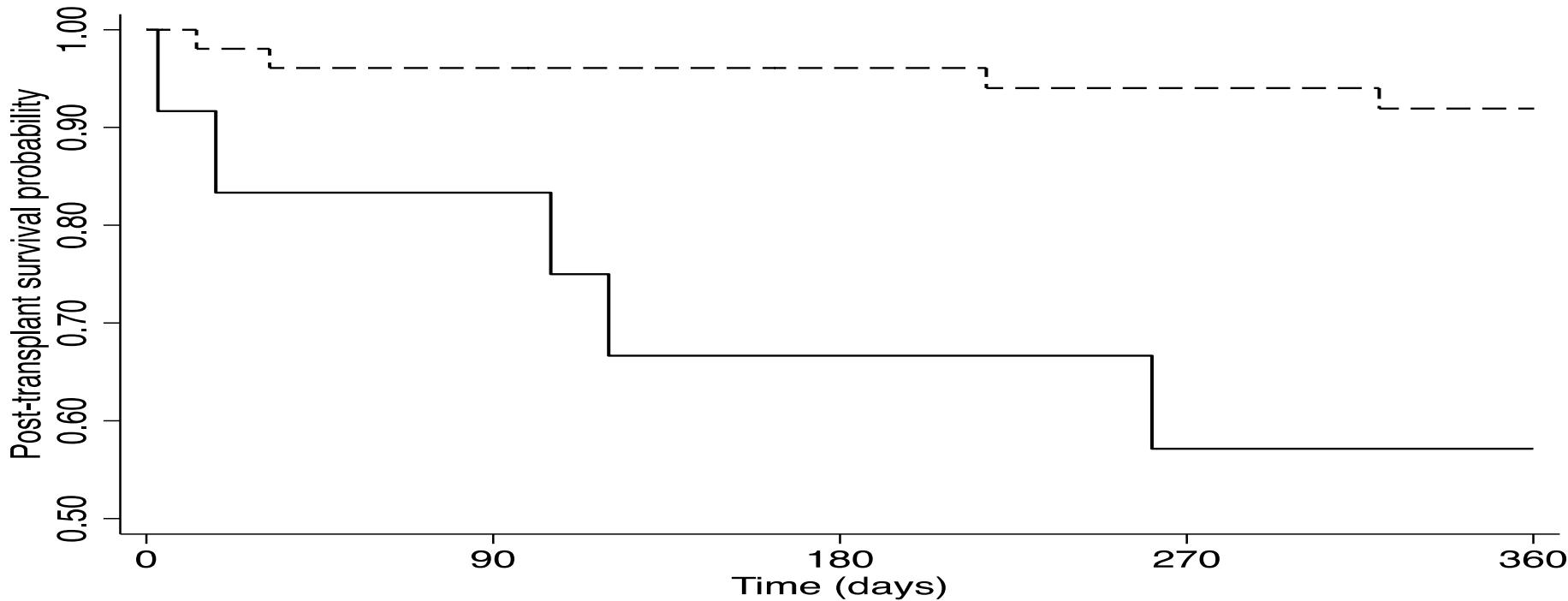
One-year post-LT survival (ACLF-3)

Variable	Yes	No
Mechanical ventilation	0.753 (0.735-0.771)	0.854 (0.842-0.850)
DRI \geq 1.7	0.781 (0.758-0.803)	0.829 (0.817-0.839)
Transplantation within 30 days of listing	0.825 (0.813-0.837)	0.781 (0.758-0.803)

Post-transplant survival probability



	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



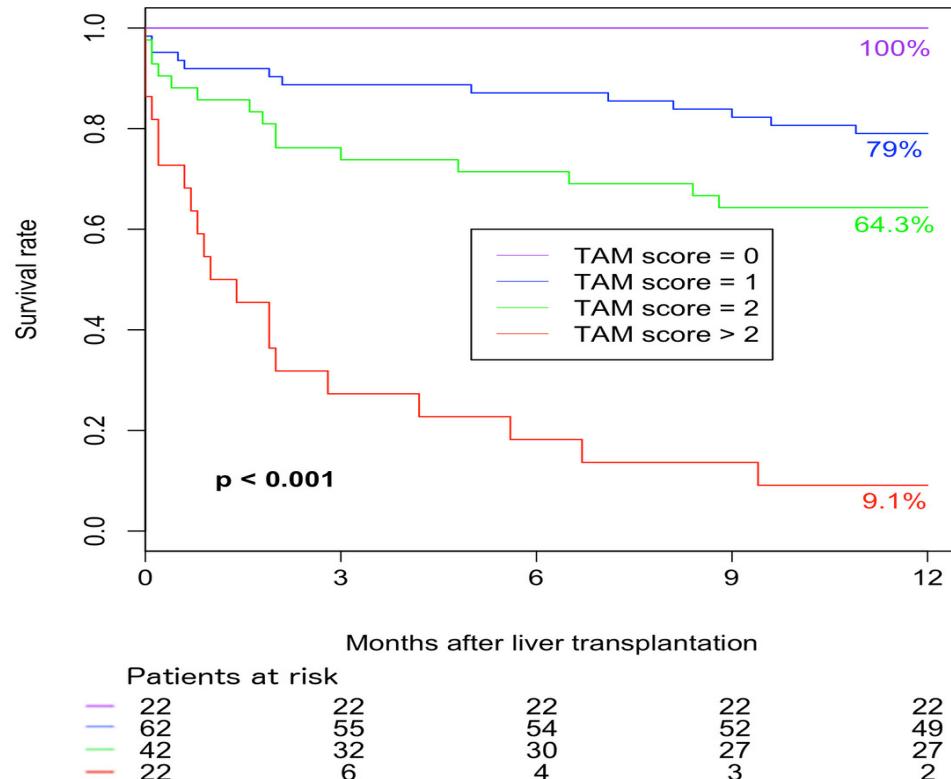
	30 days	90 days	180 days	365 days
No portal vein thrombosis	0.980 (0.869-0.972) N=51	0.961 (0.852-0.900) N=50	0.961 (0.852-0.900) N=48	0.919 (0.799-0.960) N=43
Portal vein thrombosis	0.833 (0.487-0.955) N=11	0.833 (0.487-0.955) N=11	0.667 (0.337-0.597) N=9	0.571 (0.254-0.958) N=7

Transplantation for ACLF-3 Model (TAM) score

- Multi-center study across 5 European institutions
- 152 patients transplanted with ACLF-3
- Split-sample validation (76 patients in derivation and validation cohort)
- 22 patients met outcome of 1-year mortality in derivation cohort

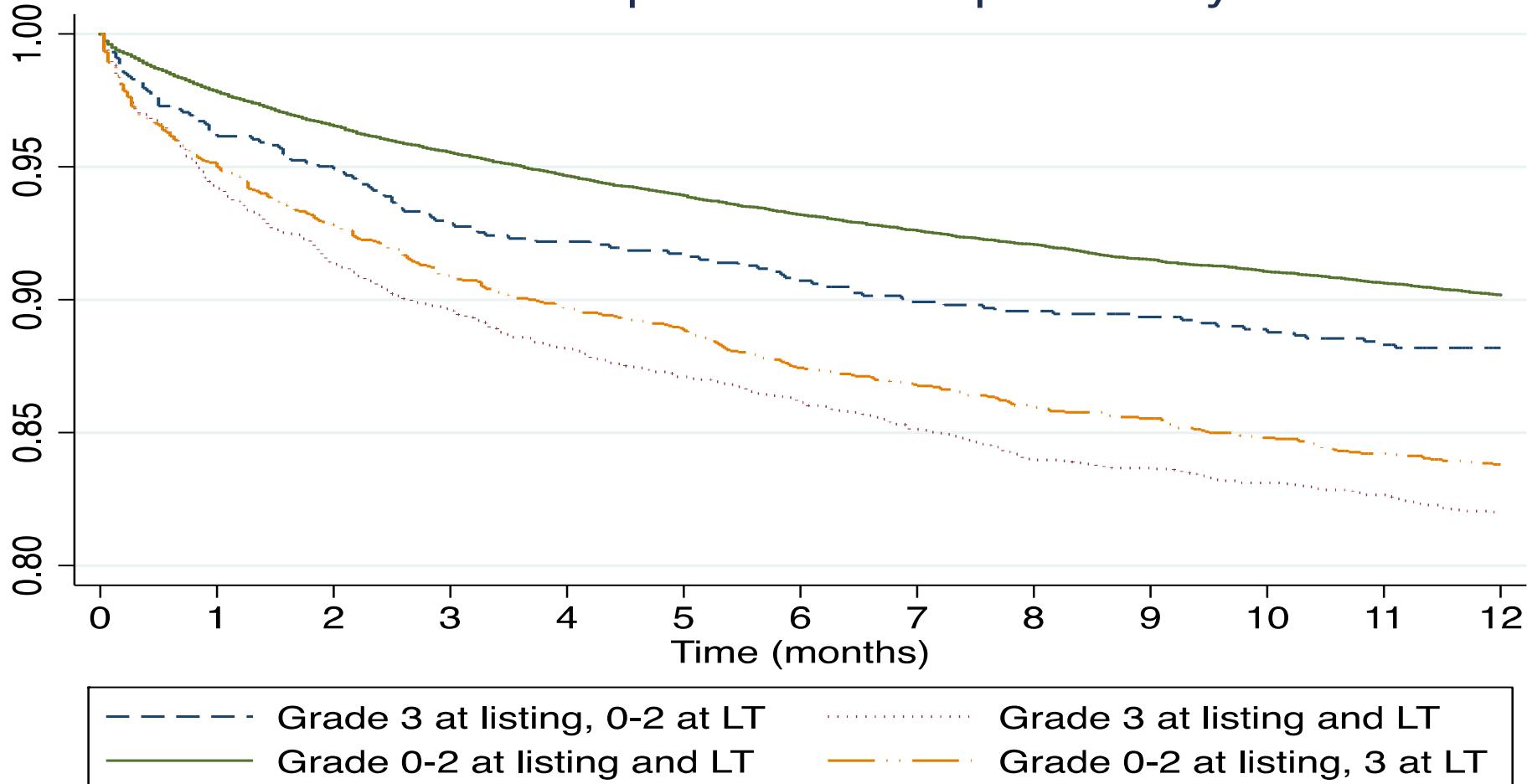
Transplantation for ACLF-3 Model (TAM) score

	Points
Arterial lactate level (mmol/l)	
<4	0
≥4	1
Mechanical ventilation with $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 200 mm Hg	
No	0
Yes	1
Age (years)	
<53	0
≥53	1
Leukocyte counts (G/l)	
>10	0
≤10	1
TAM score	$= \Sigma$

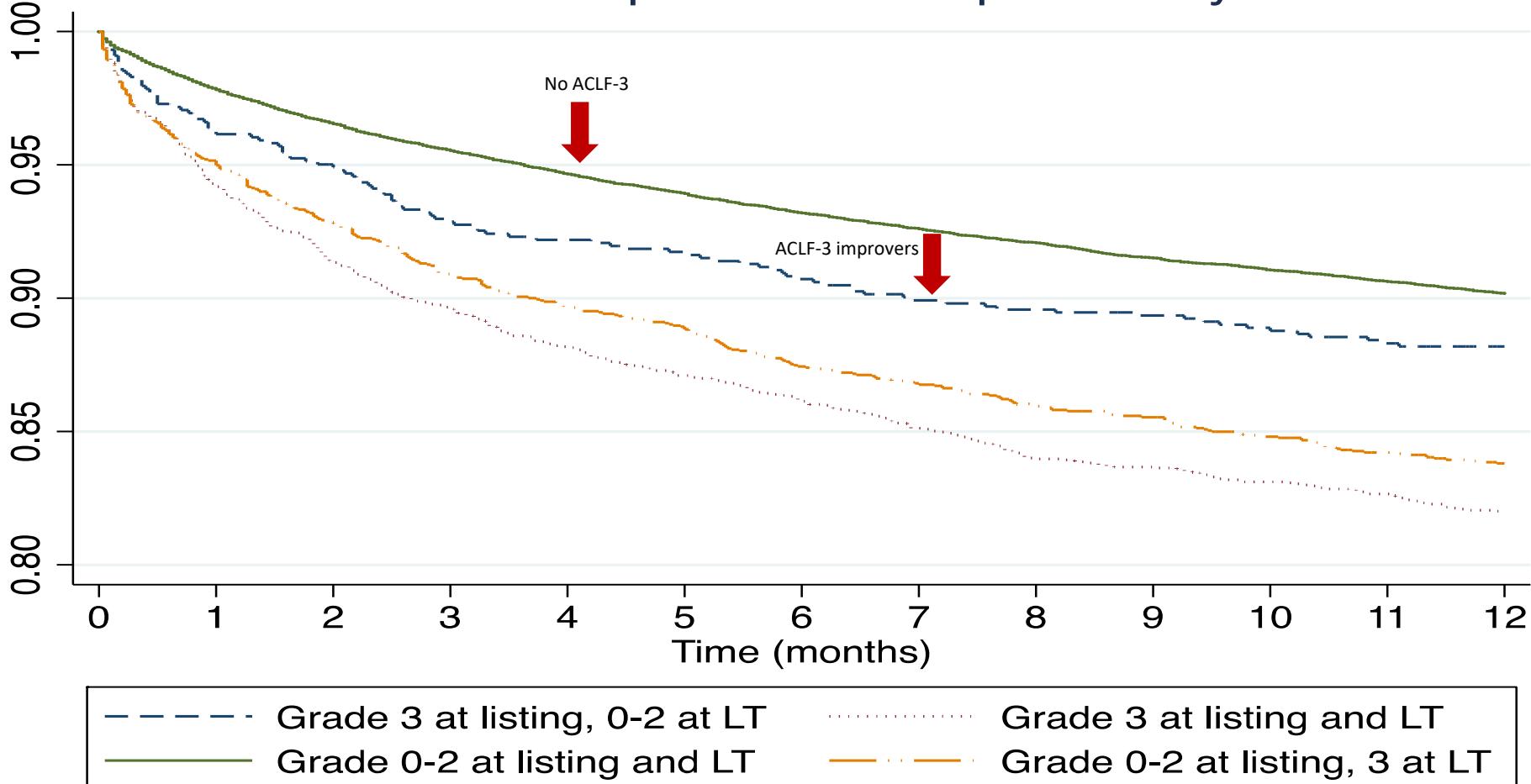


Patients selection and optimization

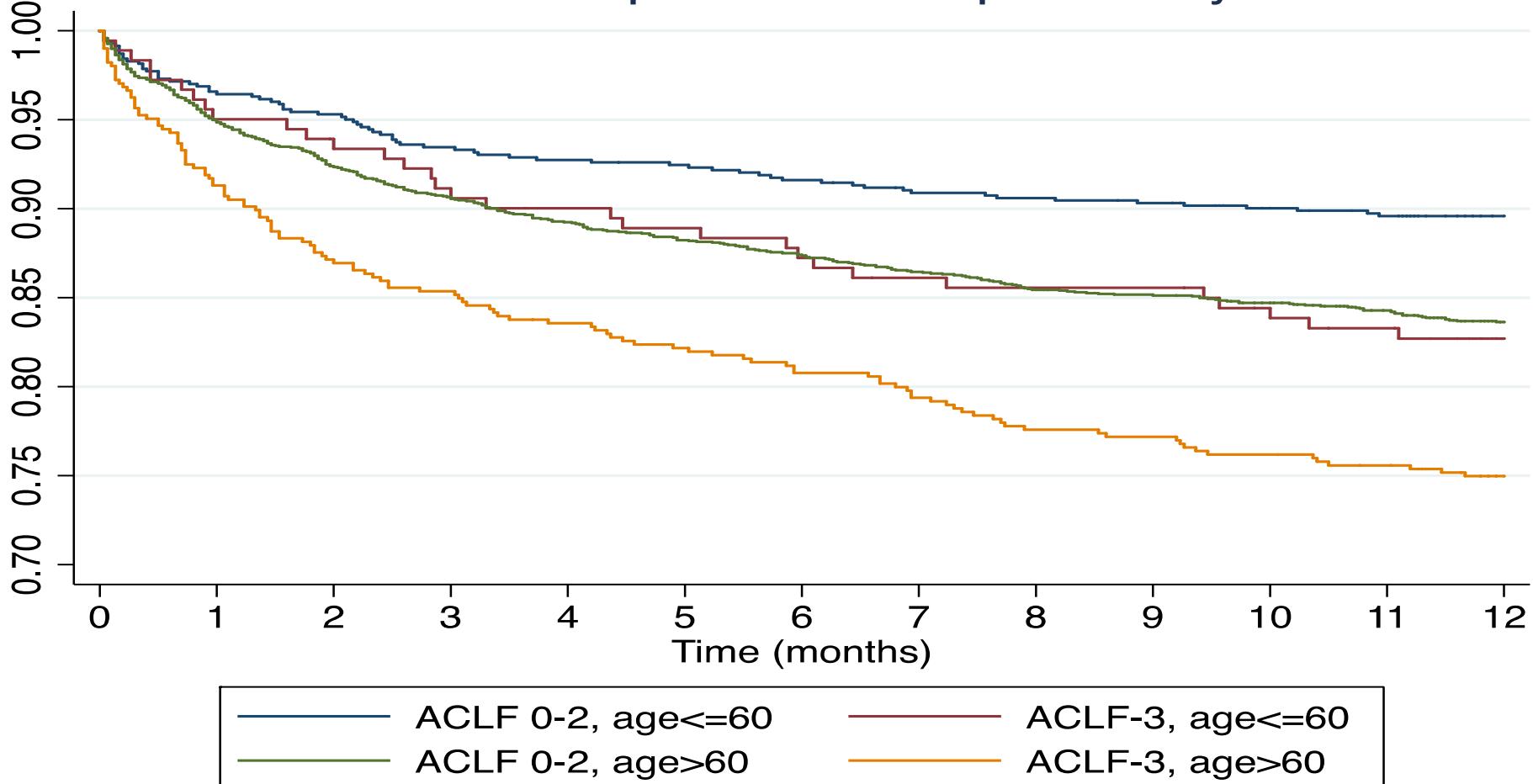
Post-transplant survival probability



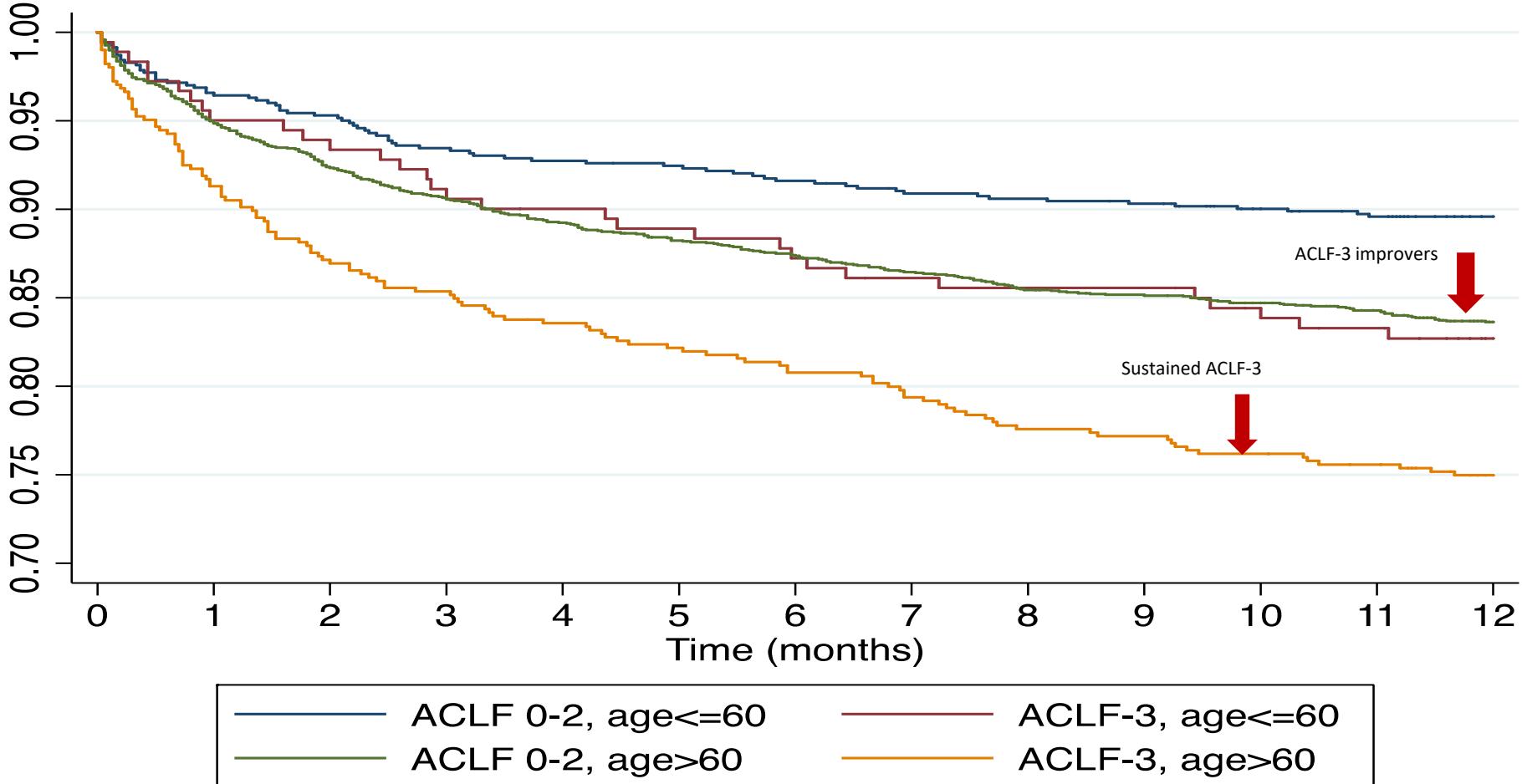
Post-transplant survival probability



Post-transplant survival probability



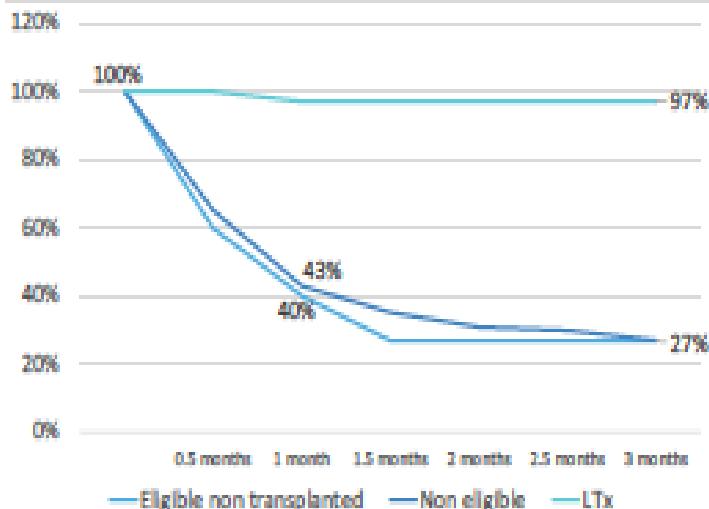
Post-transplant survival: elderly patients



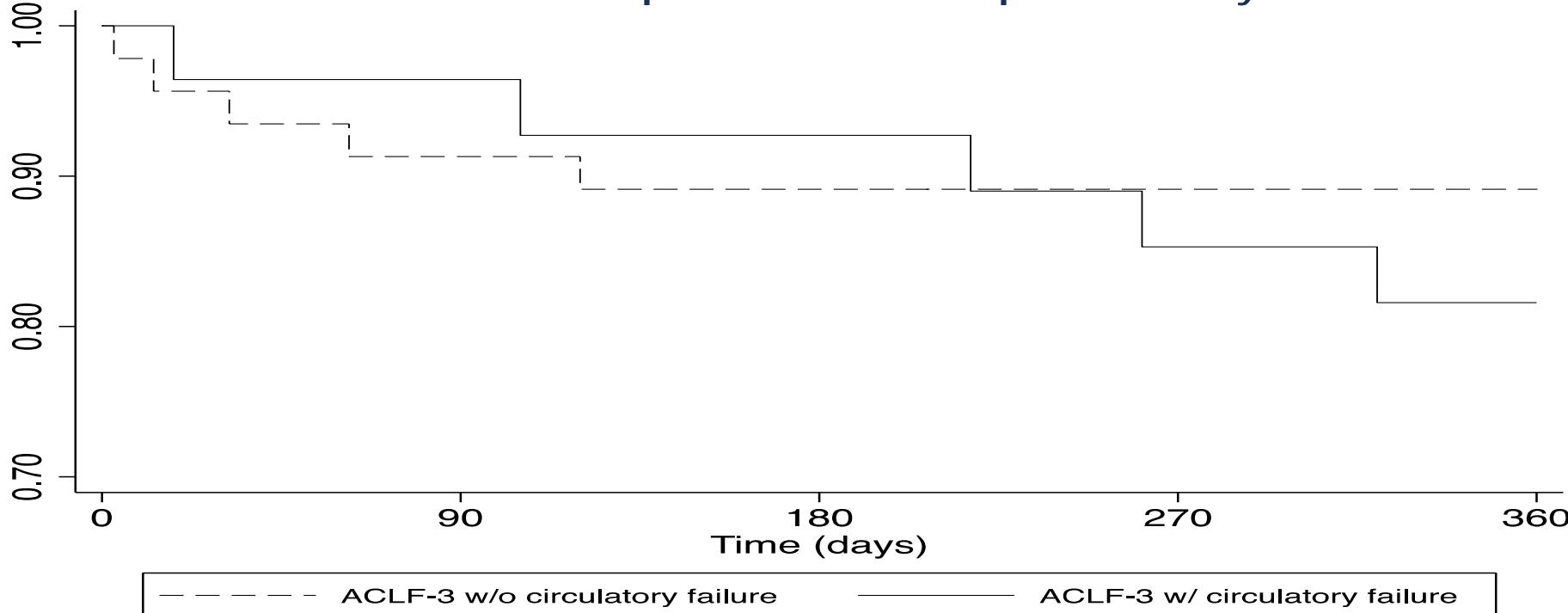
Patient Selection

- 36 patients transplanted after admission to ICU
- 25% had ACLF-3 at LT
- 97% post-LT survival at 3 months
- Factors associated with not receiving LT:
 - Age > 60 years (HR=8.95)
 - Mechanical ventilation (HR=3.32)

Figure 4: 3 months survival of LTx and non-transplanted patients



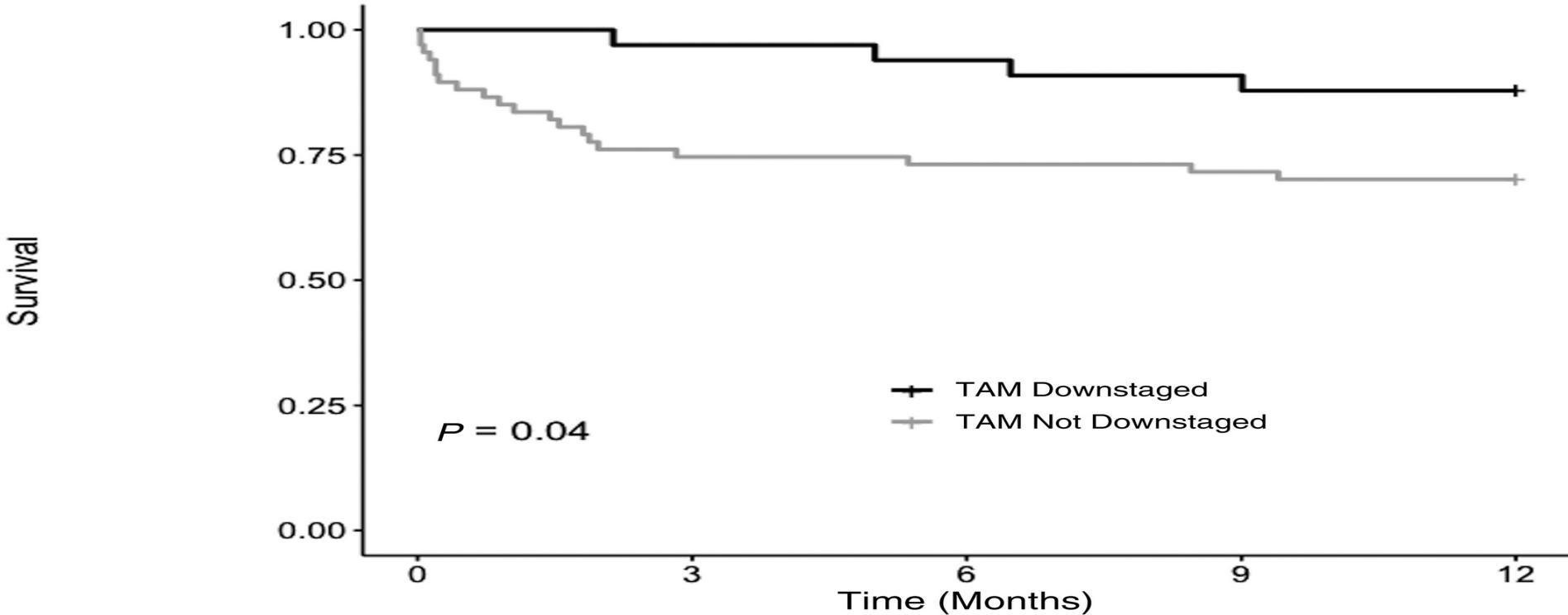
Post-transplant survival probability



	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

	Age	Vasopressor dosage	Outcome	Cause of Death
Low dose (norepinephrine ≤0.1 mcg/kg/min)	54	Norepinephrine 0.07	Dead	Sepsis
	29	Norepinephrine 0.09	Alive	
	64	Norepinephrine 0.07	Alive	
	61	Norepinephrine 0.07	Alive	
	67	Norepinephrine 0.06	Alive	
	69	Norepinephrine 0.04	Alive	
	58	Norepinephrine 0.03	Dead	HCC recurrence
	64	Norepinephrine 0.03	Dead	Cardiac arrest
	50	Vasopressin 0.04	Alive	
	65	Vasopressin 0.04	Alive	
	51	Vasopressin 0.04	Alive	
	65	Vasopressin 0.03	Alive	
	50	Vasopressin 0.03	Alive	

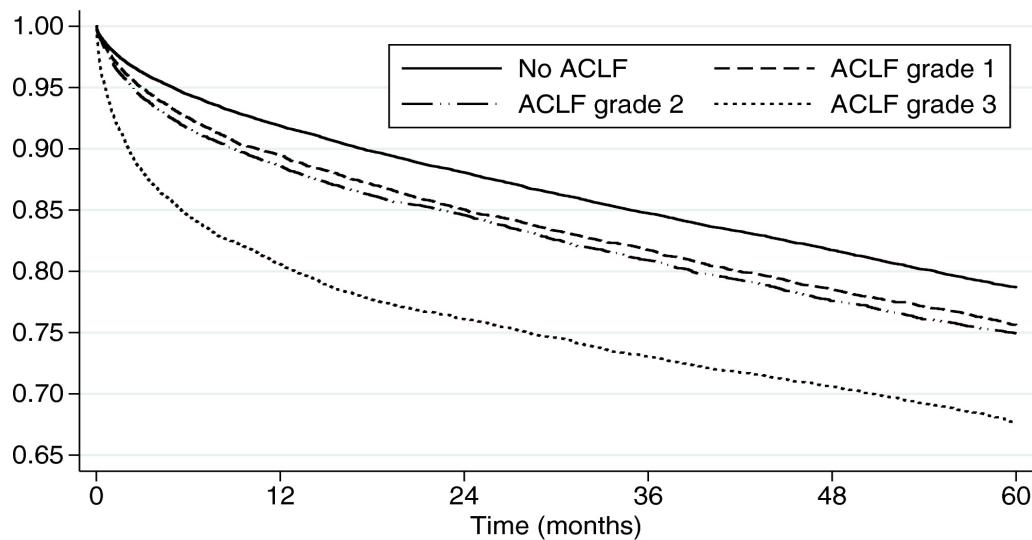
Age (years)	Vasopressor requirements	Outcome	Cause of death
63	Norepinephrine 0.24		
	Vasopressin 0.3	Alive	
	Epinephrine 0.4		
66	Norepinephrine 0.4		
	Vasopressin 0.04	Alive	
57	Norepinephrine 0.4		
	Vasopressin 0.03	Alive	
55	Norepinephrine 0.3		
	Vasopressin 0.04	Dead	Sepsis
Moderate dose (norepinephrine > 0.1 mcg/kg/min or multiple vasopressors)	Norepinephrine 0.3		
47	Vasopressin 0.04	Alive	
36	Norepinephrine 0.3		
	Phenylephrine 0.04	Alive	
45	Norepinephrine 0.15		
	Vasopressin 0.02	Alive	
69	Epinephrine 0.4		
	Vasopressin 0.03	Alive	
65	Norepinephrine 0.19		
39	Norepinephrine 0.18		
45	Phenylephrine 0.15		
55	Norepinephrine 0.12		
	Vasopressin 0.02	Dead	Sepsis
66	Norepinephrine 0.12		
	Vasopressin 0.02	Alive	
52	Norepinephrine 0.15		
55	Norepinephrine 0.15		
47	Norepinephrine 0.12		



Outcomes beyond short-term survival

Long-term outcomes

Posttransplant patient survival probability



Primary cause of death after 1 year:

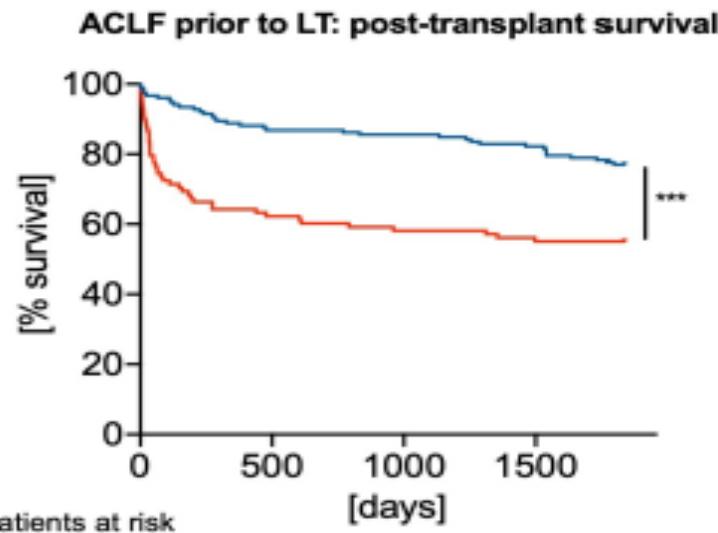
No ACLF: infection (29.3%), malignancy (28.6%)

ACLF-1: infection (32%), malignancy (21.6%)

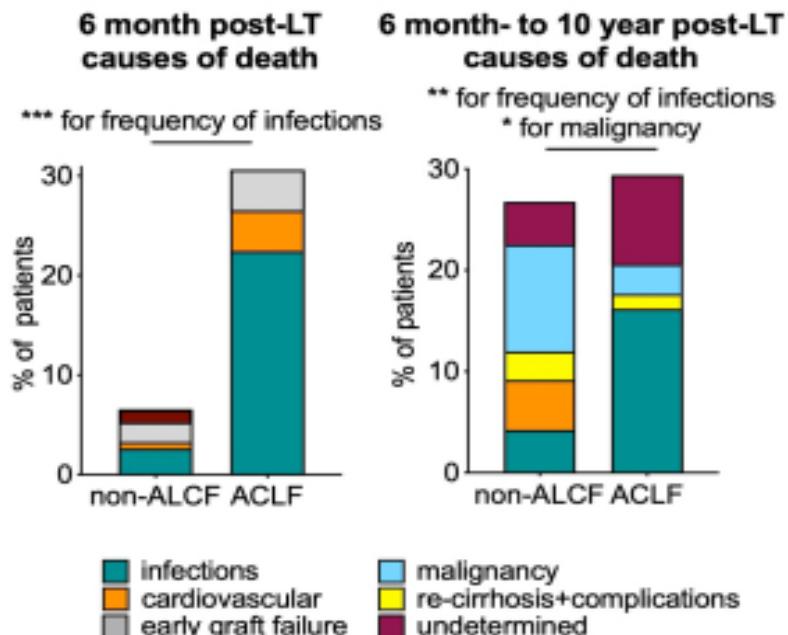
ACLF-2: infection (33.9%), malignancy (20.2%)

ACLF-3: infection (37.6%), malignancy (18.4%)

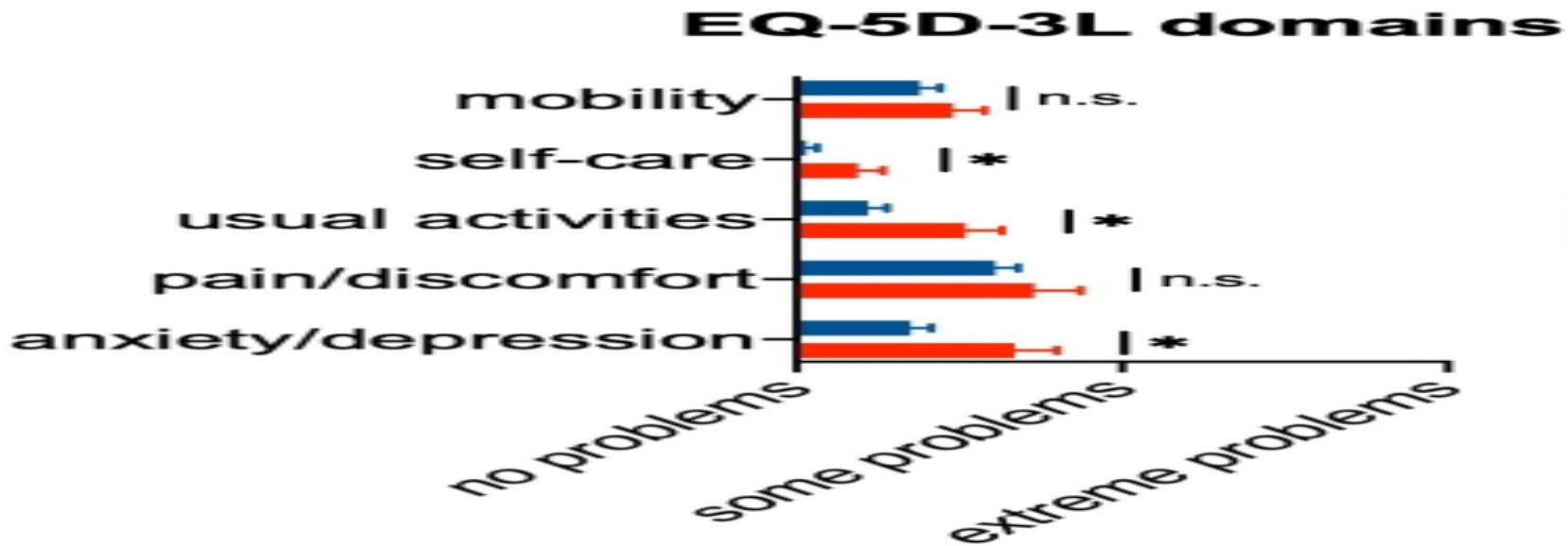
Post-LT survival and complications



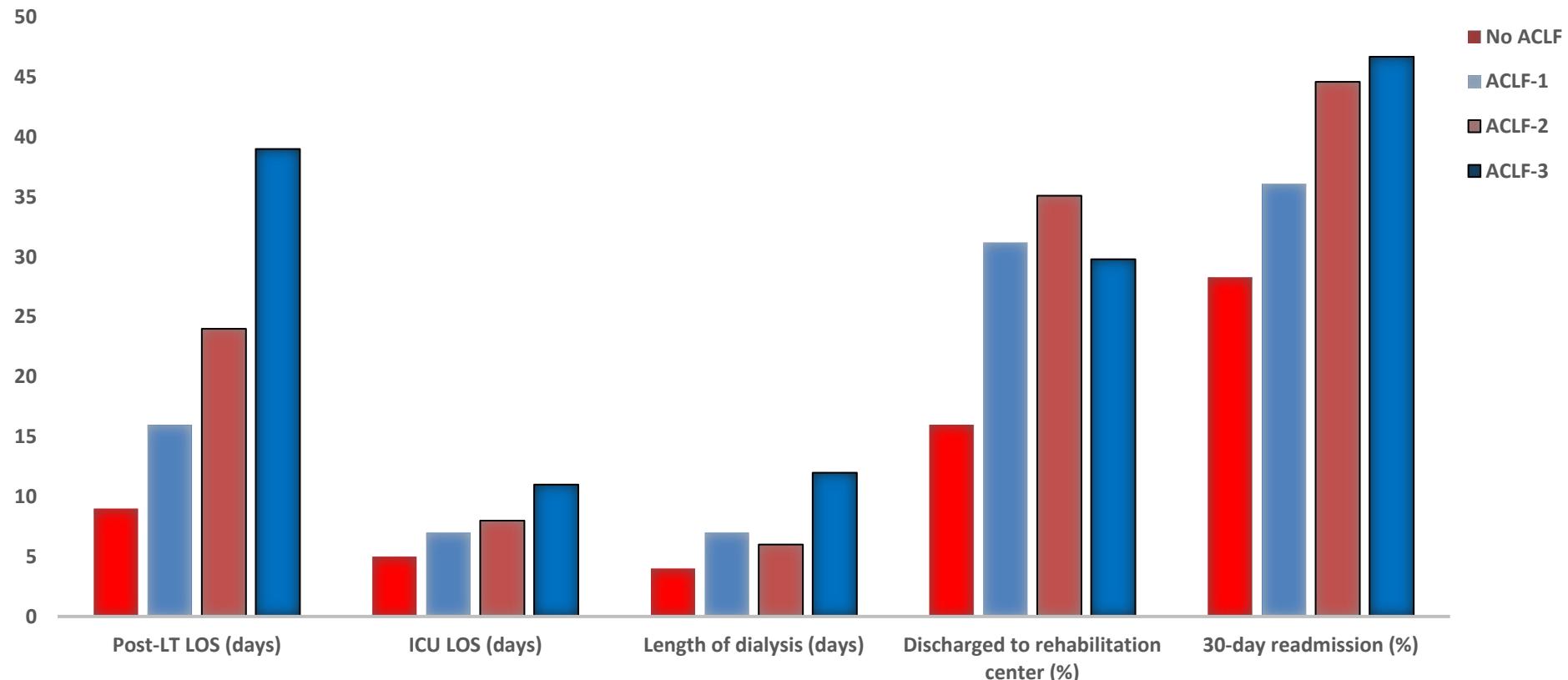
Non-ACLF	152		118
ACLF	98		54



Quality of Life



Resource Utilization



Summary

- ACLF is a syndrome of systemic inflammation and organ system failure in the setting of a precipitant, distinct from decompensated cirrhosis
- Liver transplantation can yield 1-year survival outcomes above 80%
 - Mechanical ventilation/respiratory failure, high DRI organ, portal vein thrombosis, elevated arterial lactate level may portend poor outcomes
- MELD-Na score does not fully reflect mortality in the setting of ACLF

Future Directions

- Should patients with severe ACLF receive priority for donor organs?
 - Spanish and UK ACLF transplantation tier policy since 2021
- In which patients with severe ACLF is liver transplantation futile?
 - Multi-national CHANCE study will prospectively collect survival data
- Do patients transplanted with severe ACLF have adequate survivorship after transplantation?