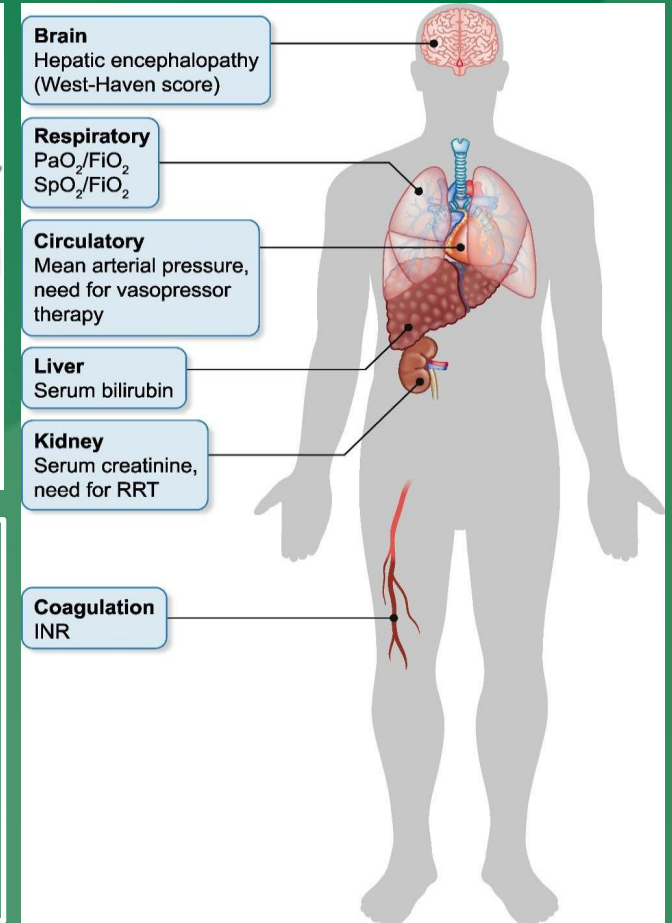
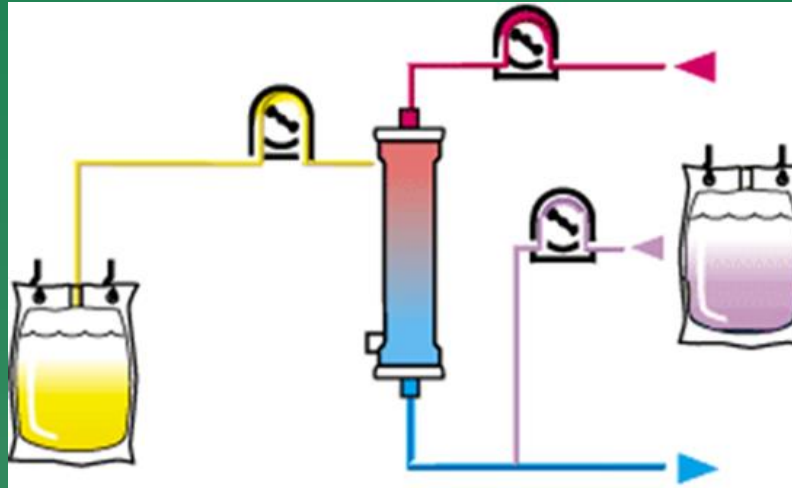




Bridging the acute-on-chronic liver failure (ACLF) patient through liver transplantation.



Constantine J. Karvellas MD SM FRCPC FCCM

Professor

Department of Critical Care Medicine

Adjunct, Department of Medicine (Liver Unit)

University of Alberta

Andre-Viallet 2026

Conflits d'intérêts potentiels

Nature des relations	Nom de l'organisation à but lucratif ou sans but lucratif
Les paiements directs incluant les honoraires	Vantive, Genfit, Mallinckrodt, Miromatrix (DSMB), Morphocell, Cytotherix
La participation à des comités consultatifs ou des bureaux de conférenciers	
Le financement de subventions ou d'essais cliniques	
Les brevets sur un médicament, un produit ou un appareil	
Tout autre investissement ou toute autre relation qu'un participant raisonnable et bien informé pourrait considérer comme un facteur d'influence sur le contenu de l'activité éducative	

CanMEDS Roles



X	Medical Expert (As Medical Experts, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centred care. Medical Expert is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
X	Communicator (As Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
X	Collaborator (As Collaborators, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
X	Leader (As Leaders, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
X	Health Advocate (As Health Advocates, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
X	Scholar (As Scholars, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
X	Professional (As Professionals, physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

Objectives: Acute on chronic Liver Failure (ACLF)

1. Understand the definition of Acute-on-chronic liver failure (ACLF)
2. Review the critical care management of ACLF examining specific organ failure
3. Review current management of acute kidney injury and hepatorenal syndrome in ACLF
4. Review the challenges with determining futility in ACLF regarding 'too sick to transplant'



What Is Acute-on-Chronic Liver Failure (ACLF)?

EASL-AASLD Consensus Group

an acute decompensation (AD) of hepatic function in cirrhotic patients, either secondary to superimposed liver injury or due to system precipitating factors culminating in multiple organ dysfunction and associated with increased mortality at 3 months



ACLF: APASL, EASL-CLIF and NACSELD

Failing organ	Asian Pacific Association for the Study of the Liver organ failures definition	European Association for the Study of the Liver-Chronic Liver failure organ failures definition	North American Consortium for Study of End-stage Liver Disease organ failures definition
Liver	Total bilirubin ≥ 5 mg/dL and INR ≥ 1.5	Bilirubin level of >12 mg/dL	—
Kidney	Acute Kidney Injury Network criteria	Creatinine level of ≥ 2.0 mg/dL or renal replacement	Need for dialysis or other forms of renal replacement therapy
Brain	West-Haven hepatic encephalopathy grade 3-4	West-Haven hepatic encephalopathy grade 3-4	West-Haven hepatic encephalopathy grade 3-4
Coagulation	INR ≥ 1.5	INR ≥ 2.5	—
Circulation	—	Use of vasopressor (terlipressin and/or catecholamines)	Presence of shock defined by mean arterial pressure <60 mm Hg or a reduction of 40 mm Hg in systolic blood pressure from baseline, despite adequate fluid resuscitation and cardiac output
Respiration	—	$\text{PaO}_2/\text{FiO}_2$ of ≤ 200 or $\text{SpO}_2/\text{FiO}_2$ of ≤ 214 or need for mechanical ventilation	Need for mechanical ventilation



ACLF Triggers

	CANONIC n=303, n (%)	Shi et al n=405, n (%)
Exacerbation hepatitis B	—	145 (35.8)
Bacterial infection	98 (32.6)	113 (27.9)
GI hemorrhage	40 (13.2)	40 (9.8)
Active alcoholism within the past 3 months	69 (24.5)	25 (6.1)
Other (TIPSS, surgery, large volume paracentesis without albumin, hepatitis, alcoholic hepatitis)	25 (8.6)	9 (2)
Not identifiable	126 (43.6)	8. (20.4)
More than one	39 (13.5)	36 (8.9)

CANONIC, EASL-CLIF Acute-on-Chronic Liver Failure in Cirrhosis; TIPSS, transjugular intrahepatic portosystemic shunt.
Hernaez R, et al. *Gut*. 2017;66:541–553.

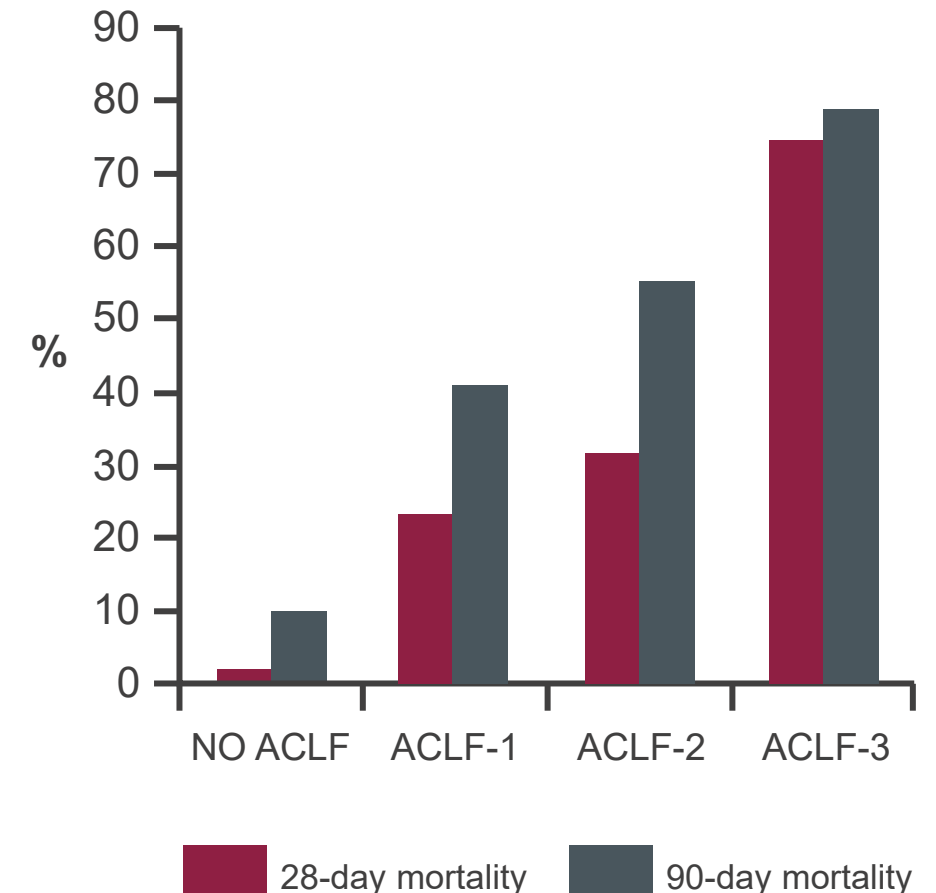


ACLF Grade and Mortality

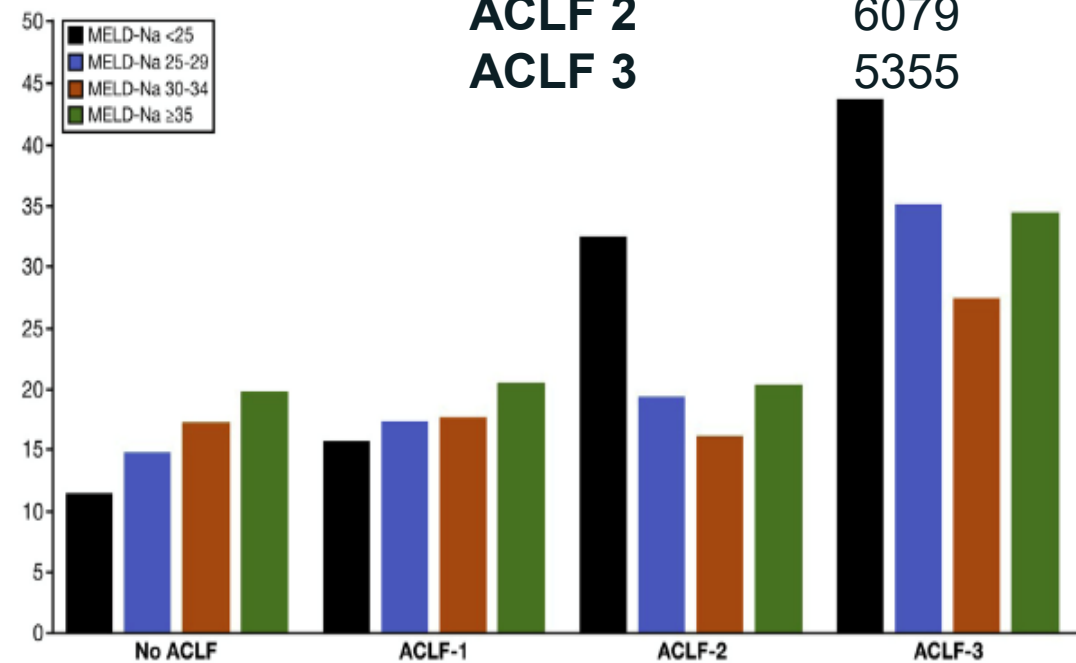
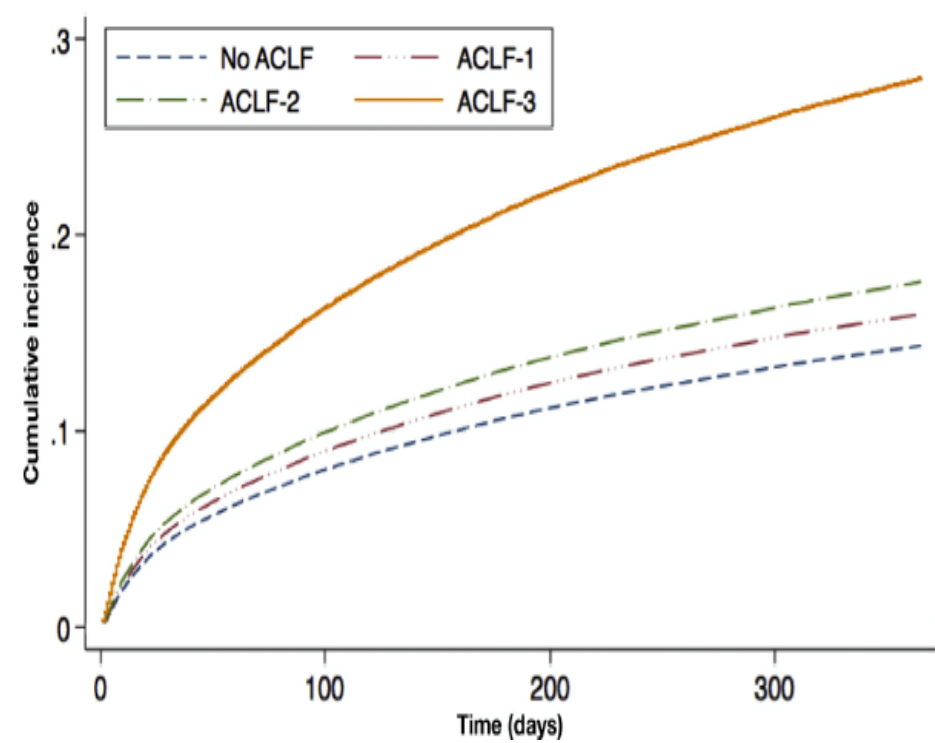
Acute-on-Chronic Liver Failure Is a Distinct Syndrome That Develops in Patients With Acute Decompensation of Cirrhosis

RICHARD MOREAU,¹ RAJIV JALAN,² PERE GINES,³ MARCO PAVESI,⁴ PAOLO ANGELI,⁵ JUAN CORDOBA,⁶ FRANCOIS DURAND,¹ THIERRY GUSTOT,⁷ FAOUZI SALIBA,⁸ MARCO DOMENICALI,⁹ ALEXANDER GERBES,¹⁰ JULIA WENDON,¹¹ CARLO ALESSANDRIA,¹² WIM LALEMAN,¹³ STEFAN ZEUZEM,¹⁴ JONEL TREBICKA,¹⁵ MAURO BERNARDI,⁹ and VICENTE ARROYO,³ for the CANONIC Study Investigators of the EASL-CLIF Consortium

- N = 1343 hospitalized patients with cirrhosis and AD
 - 303 had ACLF on admission; 112 later developed ACLF
- No ACLF
 - Patients with no organ failure
 - Patients with single hepatic, coagulation, circulation or respiratory failure, serum creatinine <1.5 mg/dL and no hepatic encephalopathy (HE)
 - Patient with cerebral failure and serum creatinine <1.5 mg/dL
- ACLF 1
 - Patients with renal failure
 - Patients with other single organ failure with
 - Serum creatinine ≥1.5 and <2 mg/dL and/or
 - HE grade 1-2
- ACLF 2
 - Patients with 2 organ failures
- ACLF 3
 - Patients with 3 or more organ failures



MELD-Na underestimates the risk of death of ACLF patients on the waiting list

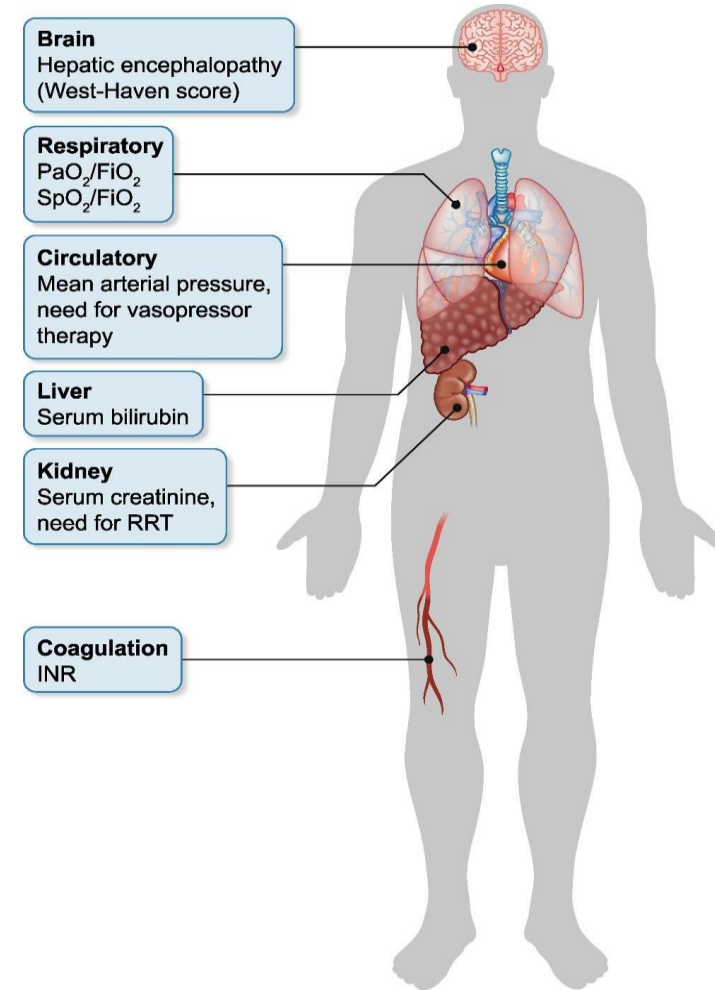


UNOS database 2005–2016

ACLF 0	79,520
ACLF 1	9640
ACLF 2	6079
ACLF 3	5355

ACLF: When to consult Critical Care?

- Respiratory management/airway protection
- Circulatory management
- Renal support
- Hematological support



Altered Mental/Status in ACLF: Not all HE

Box 1. Differential diagnosis of altered conscious level / acute confusion in ACLF.¹⁵⁹

Overt hepatic encephalopathy.
Diabetic (hyperglycaemia, ketoacidosis, hyperosmolar, lactic acidosis).
Alcohol (intoxication, withdrawal, Wernicke).
Drugs (benzodiazepines, neuroleptics, opioids).
Neuroinfections.
Electrolyte disorders (hyponatraemia and hypercalcaemia).
Nonconvulsive epilepsy.
Psychiatric disorders.
Intra-cranial bleeding and stroke.
Multi-organ failure and inflammation.
Brain lesions; traumatic, neoplasms, hydrocephalus.
Obstructive sleep apnoea.
Multiple factors may simultaneously co-exist to affect conscious level.

Intensive care management of acute-on-chronic liver failure

William Bernal^{1,*}, Constantine Karvellas², Faouzi Saliba³, Fuat H. Saner⁴,
Philippe Meersseman⁵

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Management of Altered Mental Status/HE in ACLF

1. Consider **ICU transfer** for patients with grades 3 and 4 HE (GCS < 9) along with early intubation to protect airway/avoid aspiration
2. Work-up for HE/Altered LOC should included investigation for hepatic-unrelated causes (i.e. CVA, delirium), especially if first episode of confusion or lack of response to empiric HE therapy
3. Treatment for HE in ACLF: lactulose (oral/rectal) or PEG in patients with/at risk for ileus/abdominal distention
4. Medications with short half-lives (propofol, dexmedetomidine) should be used for sedation if intubation/mechanical ventilation required
5. **Avoid serial serum ammonia level testing**

Table 2. Study Outcomes

Characteristic	Total (N = 50)	Lactulose (n = 25)	PEG (n = 25)	P Value ^a
24-h HESA score change, mean (SD)	1.1 (0.8)	0.7 (0.8)	1.5 (0.8) ^b	.002
Length of stay, d	6 (9)	8 (12)	4 (3)	.07
6- to 24-h Ammonia, mean (SD), μmol/L ^c	(n = 33)	(n = 15)	(n = 18)	
Baseline	159 (73)	175 (70)	146 (75)	.19
After study	103 (51)	82 (29)	120 (60)	.049
Difference	56 (88)	93 (71)	26 (90)	.03

Abbreviations: HESA, hepatic encephalopathy scoring algorithm; PEG, polyethylene glycol 3350–electrolyte solution.

^a Control (lactulose) and experimental (PEG) groups were compared using Wilcoxon (Mann-Whitney) rank-sum tests for ammonia and HESA score, Kaplan-Meier analysis for length of stay, and Fisher exact test for categorical variables.

^b Twenty-four hour HESA score was missing from 2 patients in the PEG group: one was competent and refused testing, the other was discharged in less than 24 h; thus, the 24-h HESA score change was calculated for 23 patients.

^c Ammonia levels at 6 to 24 hours were not available for all patients.



Causes of hypoxemia in ACLF

Specific to cirrhosis	Non-specific
Hepatic hydrothorax	Pneumonia
Hepatopulmonary syndrome (shunt)	Pulmonary embolus
α -1 antitrypsin deficiency	Pulmonary edema
Portopulmonary hypertension (right heart failure)	ARDS
	Atelectasis



Lung-Protective Strategy: ACLF and ALI

- Tidal volume = predicted body weight x 6 mL
 - Men (kg) = $50 + 2.3(\text{height in inches} - 60)$
 - Females (kg) = $45.5 + 2.3(\text{height in inches} - 60)$
- Set RR to approximate baseline minute ventilation
 - $(\text{RR} \times \text{Vt}) \sim 420 \text{ mL}$
- Set FiO_2 and PEEP to obtain SaO_2 goal of $\geq 88\%$
 - ***Higher PEEP can cause hypotension***
- Plateau pressure $< 30 \text{ cm H}_2\text{O}$
- Fluid restrictive strategy

Lower PEEP/higher FiO_2

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO_2	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24



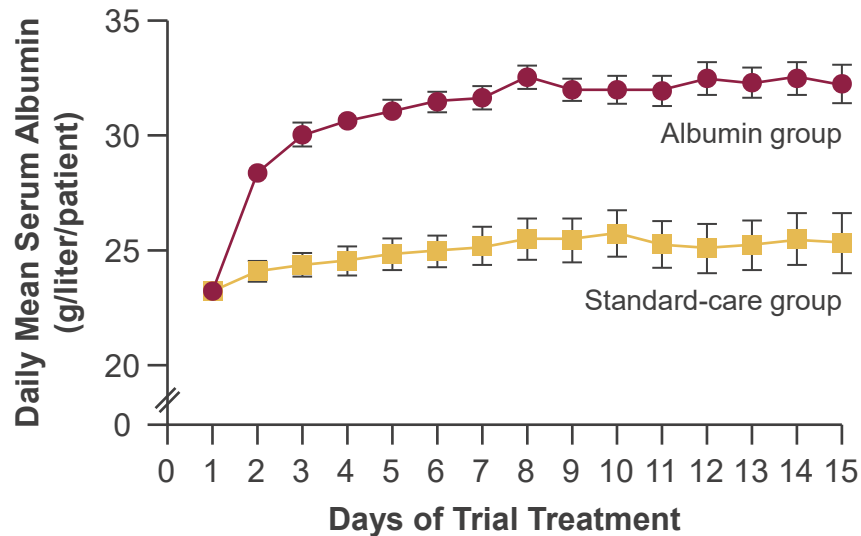
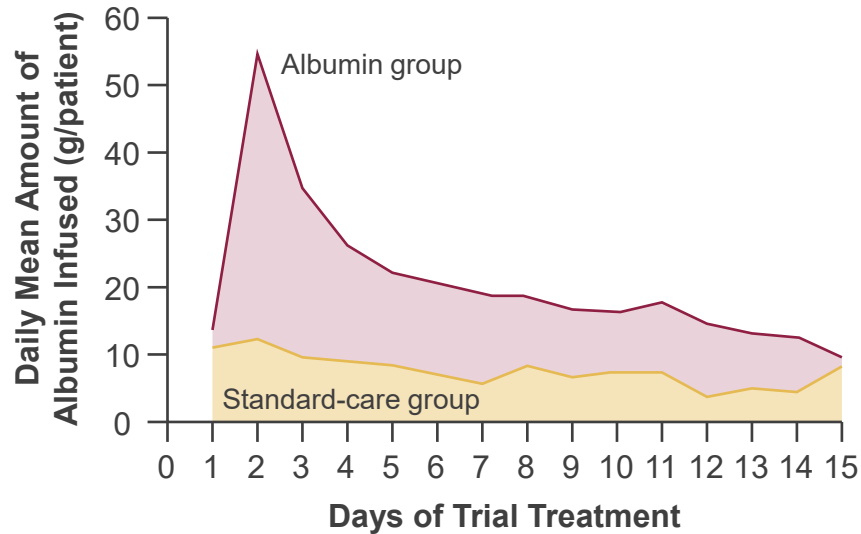
Circulatory failure/Shock



UNIVERSITY OF ALBERTA
FACULTY OF MEDICINE & DENTISTRY
Department of Critical Care Medicine

ATTIRE Trial (Decompensated Cirrhosis)

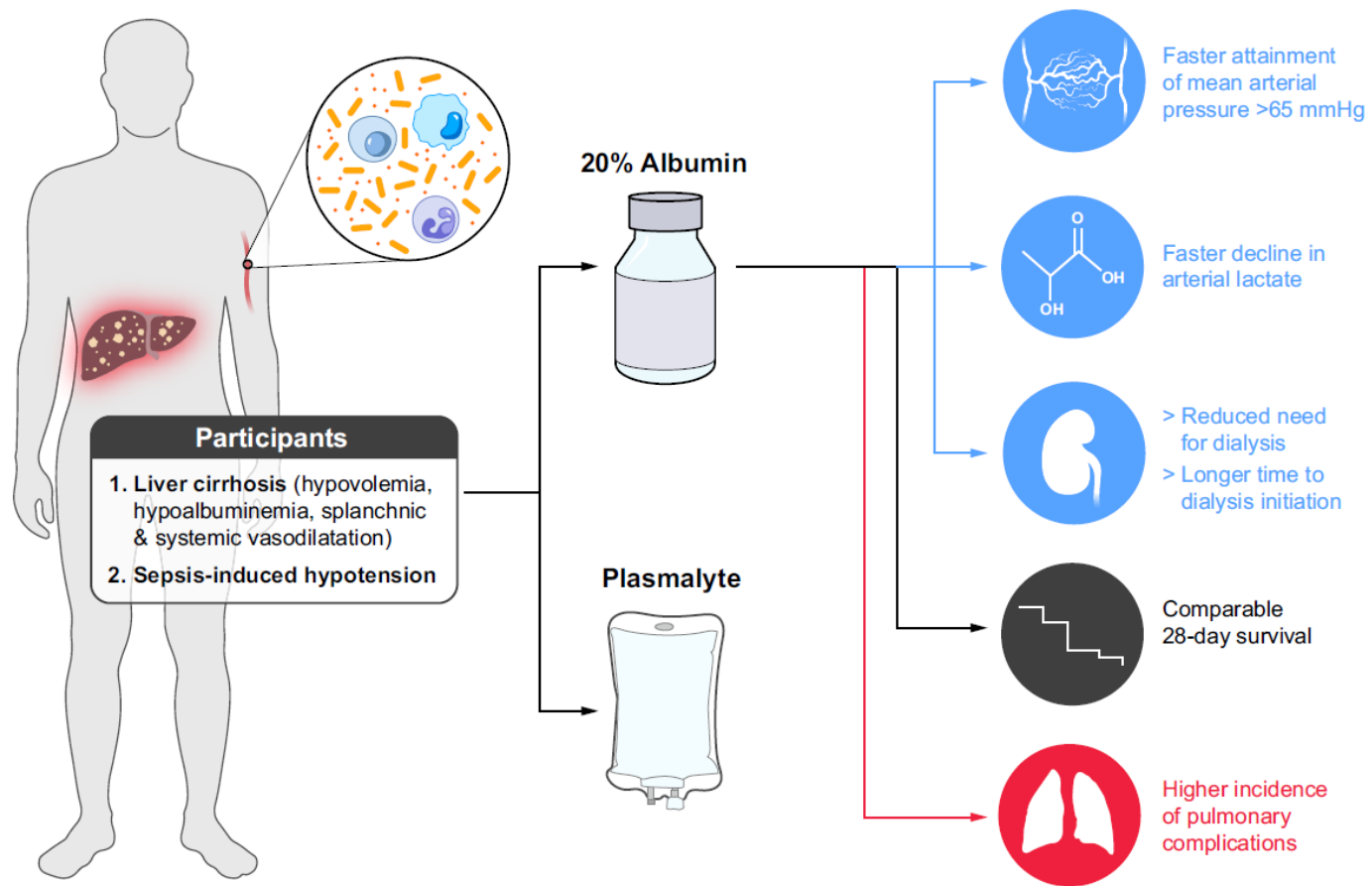
Target Serum Albumin 30 g/L vs. Standard of Care



Variable	Albumin Group (N = 380)	Standard-Care Group (N = 397)	Adjusted Odds Ratio (95% CI)	P Value
Composite primary end point — no. (%)	113 (29.7)	120 (30.2)	0.98 (0.71–1.33)	0.87
Components of composite primary end point — no. (%)				
Incidence of new infection	79 (20.8)	71 (17.9)	1.22 (0.85–1.75)	
Incidence of kidney dysfunction	40 (10.5)	57 (14.4)	0.68 (0.44–1.11)	
Incidence of death	30 (7.9)	33 (8.3)	0.95 (0.56–1.59)	
Death at 28 days	53 (14.0)	62 (15.6)	0.86 (0.57–1.30)	
Death at 3 mo	92 (24.2)	93 (23.4)	1.05 (0.74–1.48)	
Death at 6 mo	132 (34.7)	119 (30.0)	1.27 (0.93–1.73)	
Total median albumin infused per patient (IQR) — g	200 (140–280)	20 (0–120)	143 (127–158) ^s	

1. Albumin infusions **did not reduce the incidences of infection, kidney dysfunction, and death.**
2. **More serious adverse** events occurred in the **albumin group.**
Pulmonary edema

A randomized-controlled trial comparing 20% albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension [ALPS trial]



- 20% albumin is superior to plasmalyte in reversing sepsis-induced hypotension in critically ill patients with cirrhosis.
- 20% albumin does not provide survival benefit over plasmalyte.
- 20% albumin causes more pulmonary complications than plasmalyte.
- Patients with pneumonia, higher arterial lactate and SOFA score are at higher risk of pulmonary complications after 20% albumin.
- Plasmalyte is a safer fluid for resuscitation of critically ill patients with cirrhosis, pneumonia and lower serum bicarbonate.

- “reduced need for RRT” $p=0.16$,
- “longer time in hours to initiate RRT $p= 0.06$ ”

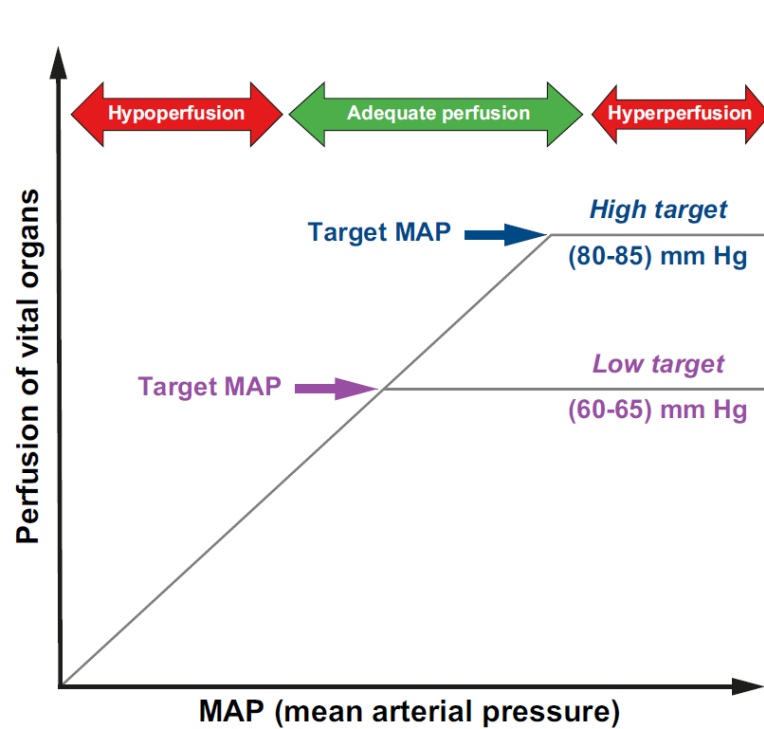
Methods: Critically ill patients with cirrhosis underwent open-label randomization to receive either 20% albumin (0.5-1.0 g/kg over 3 hours; n = 50) or plasmalyte (30 ml/kg over 3 hours, n = 50). The primary endpoint of the study was the attainment of mean arterial pressure (MAP) above 65 mmHg at 3 hours.

Rakhi Maiwall^{1,#}, Abhinav Kumar^{1,#}, Samba Siva Rao Pasupuleti², Ashini Kumar Hidam⁵,
Harshvardhan Tevethia¹, Guresh Kumar³, Amrish Sahney¹, Lalita Gouri Mitra⁴,
Shiv Kumar Sarin^{1,*}

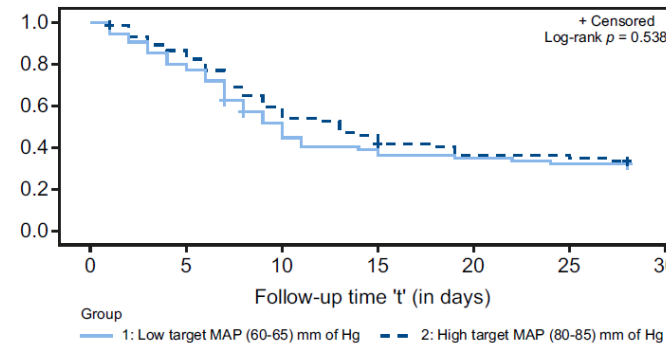
Assessment of Volume Status/Cardiac Output? ECHO

		Remarks/limitations in general ICU	Remarks/limitations in ACLF
Bedside echocardiography • LV/RV function, pulmonary pressures (TR jet) • Response to fluid	Clinical - Lactate - S(c)VO₂ - Mottling score		Decreased Lactate clearance Increased due to hyperdynamic state Score >1 associated with 100% mortality
CVP monitoring • Adequacy of perfusion ~ CVP 8-12 • Mixed venous saturation (ScvO₂ > 70%)	Static measures - CVP - PCWP - GEDVI - EVLWI - TTE: Left ventricular end-diastolic area	Poor correlation with fluid responsiveness; influenced by ventilation settings (e.g. high peep) Invasive; poor correlation with fluid responsiveness; influenced by ventilation settings (e.g. high peep) Invasive; better reflects preload than pressure markers; poor correlation with fluid responsiveness; not reliable if valve pathology Invasive; poor correlation with fluid responsiveness; unreliable in case of pulmonary embolism, lung resection, large pleural effusions; high EVLWI is a potential contraindication for extra fluid administration Absolute levels hard to interpret if no baseline data; serial measure may be useful	Unreliable if tense ascites Influenced by IAH
Other modalities • Thermodilution techniques: PiCCO, LiDCO • Lactate	Dynamic measures - SVV/PPV - Echo IVC diameter - Echo SVC diameter - Fluid challenge - PLR	Cannot be used if spontaneous breathing, cardiac arrhythmias or low tidal volume/lung compliance Cannot be used in case of spontaneous breathing, cardiac arrhythmias, low tidal volume/lung compliance Requires TEE; cannot be used in case of spontaneous breathing, cardiac arrhythmias, low tidal volume/lung compliance Requires direct measurement of CO preferably invasively; induces fluid overload if repeated Requires direct measurement of CO preferably invasively; must be performed correctly	Not validated in cirrhosis; ascites and subsequent IAH may limit their applicability and low systemic vascular resistance may alter aortic compliance, a determinant of PPV Affected by high intra-abdominal pressure TEE relatively contraindicated with esophageal varices Impact of third space loss? Unreliable with intra-abdominal hypertension

A randomised-controlled trial (TARGET-C) of high vs. low target mean arterial pressure in patients with cirrhosis and septic shock



- Decreased incidence of intradialytic hypotension
- More adverse events



No difference in 28-day mortality

- Higher incidence of intradialytic hypotension
- Less adverse events

Highlights

- A higher target MAP strategy does not confer any survival benefit in patients with cirrhosis and septic shock.
- A higher target MAP strategy was associated with more frequent adverse events.
- This strategy was associated with decreased incidence of intradialytic hypotension, better tolerance of dialysis, and improved renal recovery.
- A higher target MAP strategy can be considered alongside careful monitoring for adverse events.

Cirrhosis with septic shock? High MAP- Splanchnic vasodilatation or low MAP-chronic adaptation

Authors

Rakhi Maiwall, Samba Siva Rao Pasupuleti, Ashini Kumar Hidam, ..., Rajendra Prasad Mathur, Guresh Kumar, Shiv Kumar Sarin



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Assessment/Management of Shock in ACLF

- **Perform early baseline assessment of volume/perfusion status and cardiovascular function**
- **Resuscitation of Shock: Balanced crystalloid solutions**
 - Plasmalyte, Ringer's lactate
 - Albumin: If evidence of SBP, HRS-AKI or LVP required but not as primary resuscitation fluid
- **Choice of vasopressor**
 - Norepinephrine 0.01-0.3 µg/kg/min
 - Vasopressin 0.01-0.04 IU/min (*Terlipressin 1-2 mg IV q4-6h if AKI?*)
- MAP > 65 mm Hg (**or > 75 HRS-AKI**)
- **Rule out adrenal insufficiency:** Hydrocortisone 200 mg/d (50 mg q6h IV) x 7 days or until ICU discharge for treatment of refractory shock requiring high-dose vasopressors

ACLF, Infection, and Sepsis

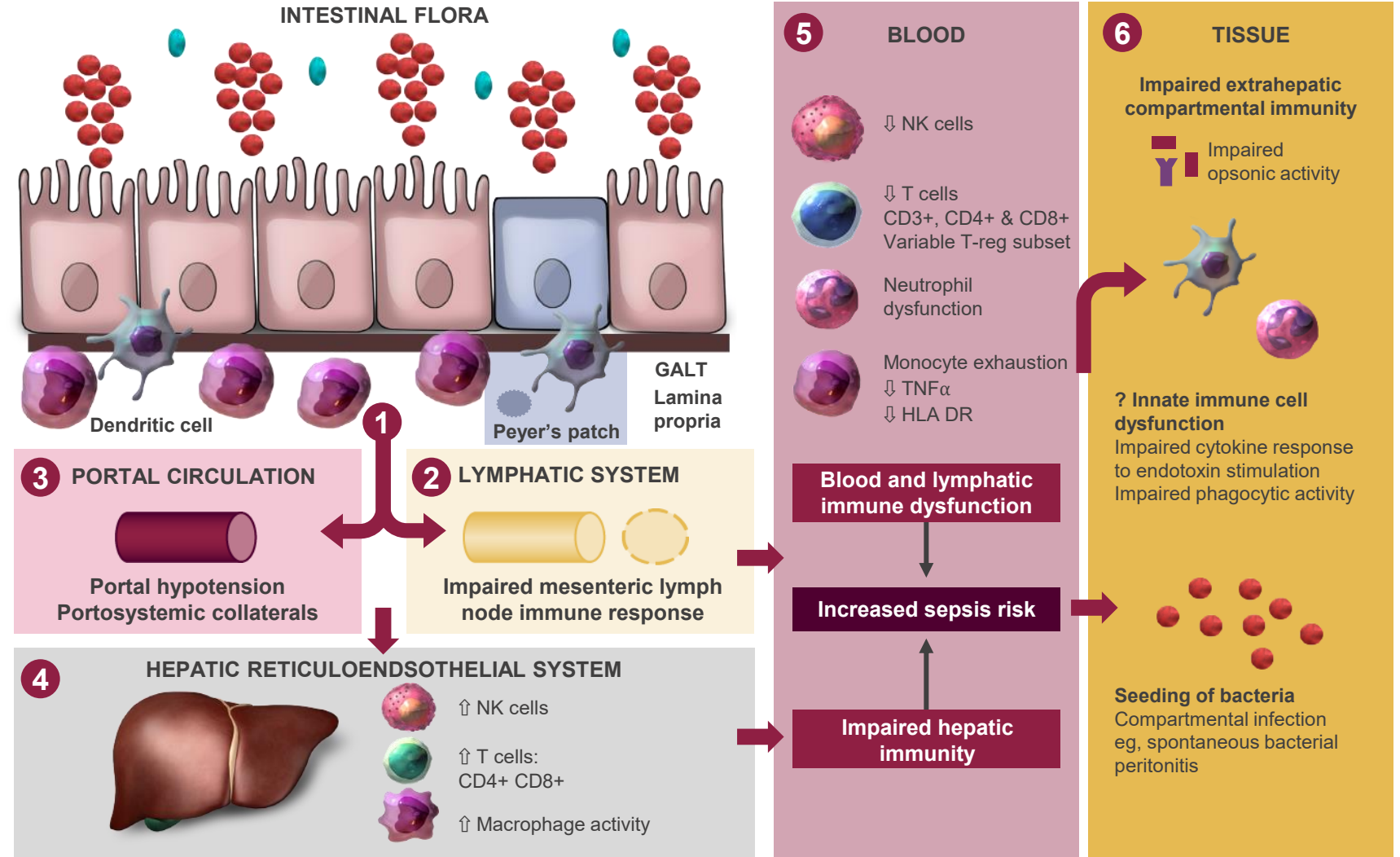
Intestinal Bacterial Overgrowth

Increased Intestinal Permeability

Impaired Local Immunity

BACTERIAL TRANSLOCATION

Dysfunctional Hepatic Immunity

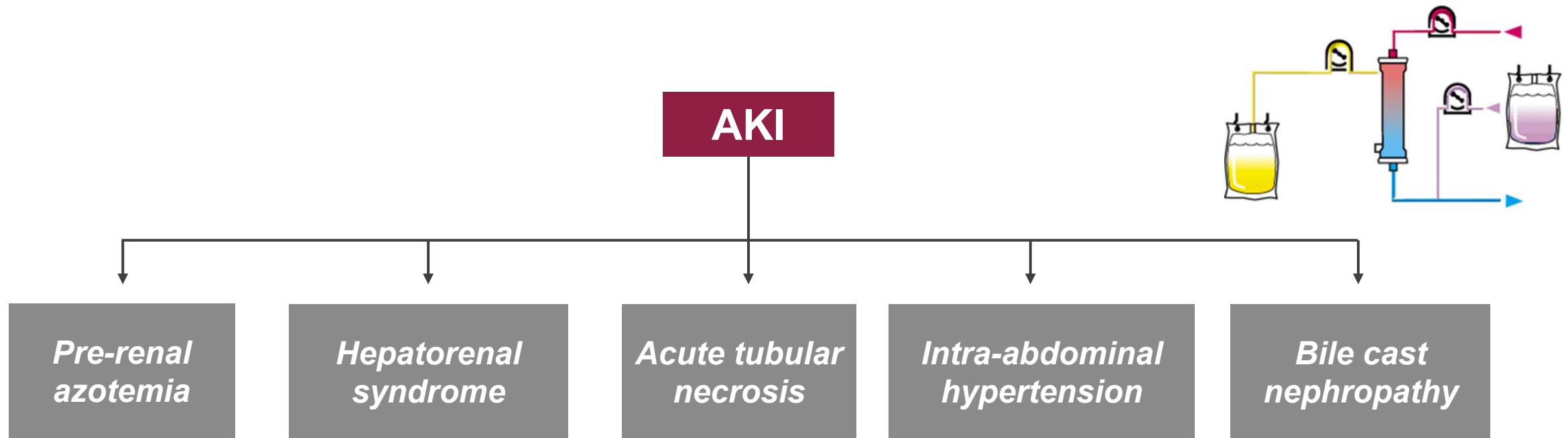


Timely Antimicrobial Therapy in Cirrhotic Patients With SBP-Associated Septic Shock

	Univariable (N=126)		Multivariable (c-statistic 0.981, N=70)	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.01 (0.97–1.05)	0.62	1.15 (0.97–1.35)	0.10
Sex (female)	1.29 (0.50–3.32)	0.59		
Bloodstream infection	3.53 (1.22–10.23)	0.02	1.07 (0.06–20.26)	0.97
Time delay to appropriate antimicrobials (h)	1.33 (1.12–1.57)	0.001	1.86 (1.10–3.14)	0.02
Lactate (mmol/L)	1.20 (1.05–1.38)	0.008	2.34 (1.04–5.29)	0.04
Number of organ failures (admission)	1.68 (1.24–2.29)	0.001	0.67 (0.27–1.69)	0.39
APACHEII (admission)	1.18 (1.09–1.28)	<0.001	1.45 (1.04–2.02)	0.03

Each hour in delay in appropriate Abx: increased mortality by 1.86

Renal Failure: Causes of Acute Kidney Injury in ACLF



- AKI in ACLF can be multifactorial, thereby posing challenges to diagnostic and therapeutic management

Prevalence and Causes of AKI in Cirrhosis/ACLF

Study	n	AKI Prevalence (%)	Hypovolaemia (%)	ATN (%)	HRS (%)
Fagundes et al., 2013	375	47	35	ND	18
Piano et al., 2013	233	27	36	ND	43
Belcher et al., 2014	110 ^a	ND	50	35	15
Alegretti et al., 2015	120 ^a	ND	33	29	30
Tandon et al., 2017	4,733	36	ND	ND	ND
Huelin et al., 2017	547	53	27	14	32

- Wide range of reported incidence influenced by definition of AKI used and patient population studied
- Revised definition of HRS-AKI based on KDIGO guidelines anticipated to increase its diagnosis

Newer Definitions of HRS-AKI Diagnostic Criteria

- Increases in serum creatinine of ≥ 0.3 mg/dL within 48 hours OR Increase in serum creatinine ≥ 1.5 times from baseline
- No response to diuretic withdrawal and 2-day fluid challenge with 1g/kg/day of albumin 20-25%
- Cirrhosis with ascites
- Absence of shock
- No current or recent use of nephrotoxic drugs (NSAIDs, contrast dye, etc)
- No signs of structural kidney injury
 - Absence of proteinuria (>500 mg/day)
 - Absence of hematuria (>50 RBCs per high power field)
 - Normal findings on renal ultrasound

New terminology and definition of HRS-AKI highlights adoption of AKI concepts related to KDIGO guidelines used in general critical care

Staging of HRS-AKI

Stage 1

Increase in serum creatinine ≥ 0.3 mg/dL or increase in serum creatinine ≥ 1.5 -fold to 2-fold from baseline

- Stage 1a: Creatinine < 1.5 mg/dL
- Stage 1b: Creatinine ≥ 1.5 mg/dL

Stage 2

Increase in serum creatinine at least 2-fold to 3-fold from baseline

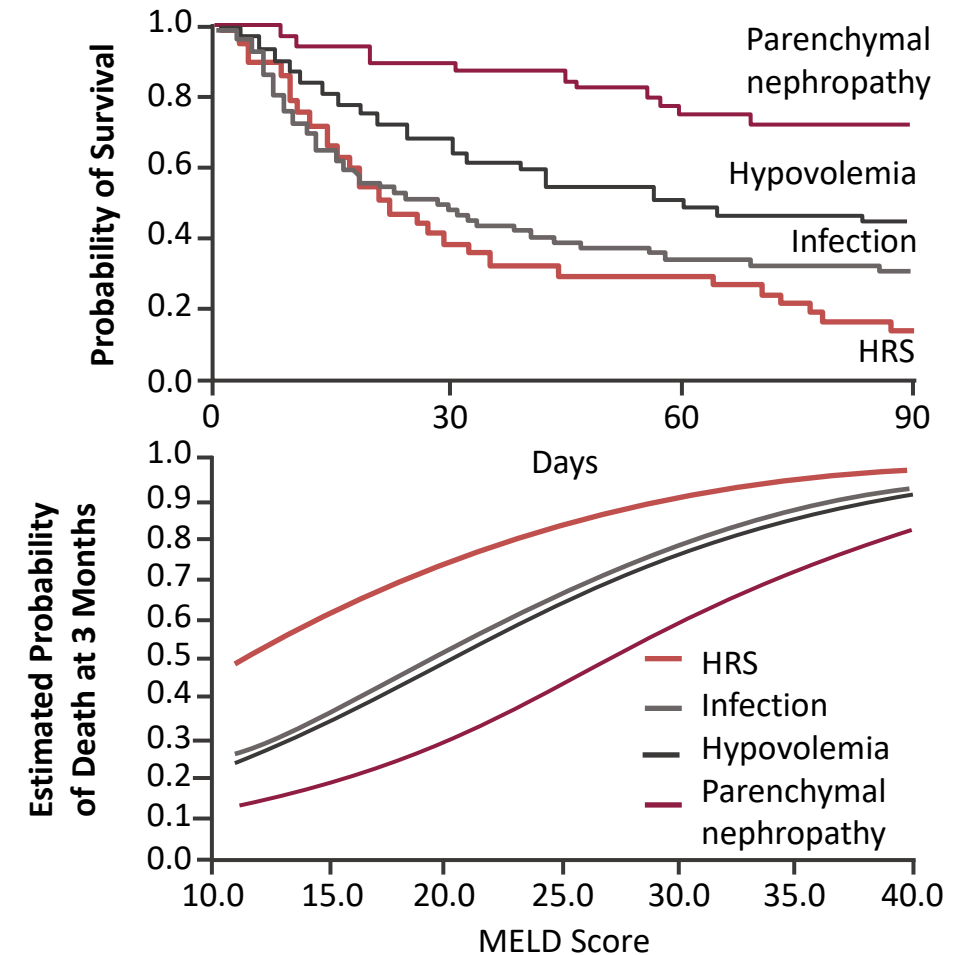
Stage 3

Increase in serum creatinine at least 3-fold from baseline or serum creatinine ≥ 4.0 mg/dL with an acute increase ≥ 0.3 mg/dL or initiation of RRT

- Of note, urine output currently not included in the staging criteria¹
- However, study in cirrhotic ICU cohort incorporating urine output (in addition to SCr) demonstrated higher incidence & severity of HRS-AKI²

Significance of the etiology of AKI in cirrhosis

- 562 cirrhotic patients over 6-year period
 - AKI, stratified into 4 groups
- Incidence/mortality
 - Infection/sepsis (46%; 69%)
 - Hypovolemia (32%; 54%)
 - **HRS (13%; 85%)**
 - Parenchymal nephropathy (9%; 27%)
- 90-day mortality → worse for HRS
 - **Adj-HR 3.48 (1.48–8.17)**



HRS independently associated with 90-day mortality after adjusting for MELD, Na and HE



Maintaining MAP and Renal Function

- An increase in MAP is strongly associated with a decrease in SCr
- MAP increase is needed for an increase in renal function to be predicted

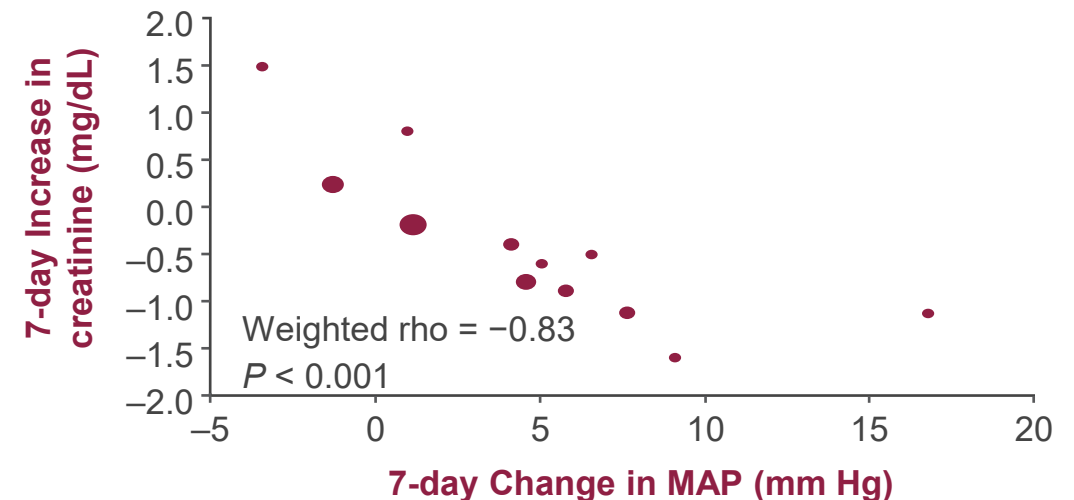
Relationship Between MAP and Kidney Function in HRS

Baseline SCr	SCr reduction required to achieve goal ^a (%)	Predicted increase in MAP to achieve desired SCr goal (mm Hg) ^b
2.0 mg/dL	25.0	3.7 (2.5 to 4.9)
2.5 mg/dL	40.0	6.1 (4.7 to 7.5)
3.0 mg/dL	50.0	8.5 (6.7 to 10.3)
3.5 mg/dL	57.1	10.9 (8.5 to 13.3)
4.0 mg/dL	62.5	13.3 (10.3 to 16.3)

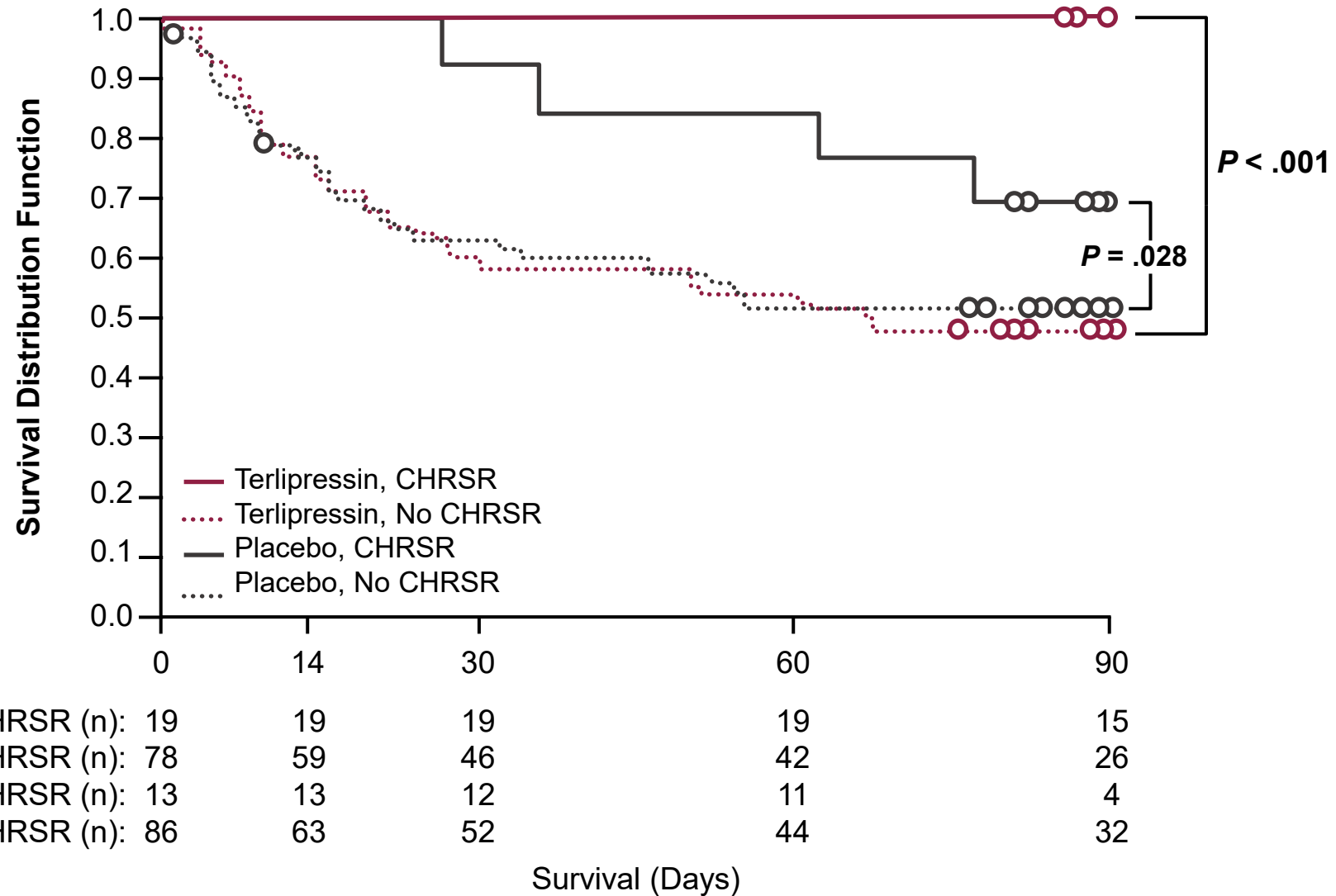
^aSCr goal is 1.5 mg/dL. ^bValues given as mean (95% confidence interval).

Velez JCQ, et al. *Am J Kidney Dis*. 2011;58:928–938.

**7-day Change in Serum Creatinine vs 7-day Change in MAP:
Only Randomized Controlled Trials**

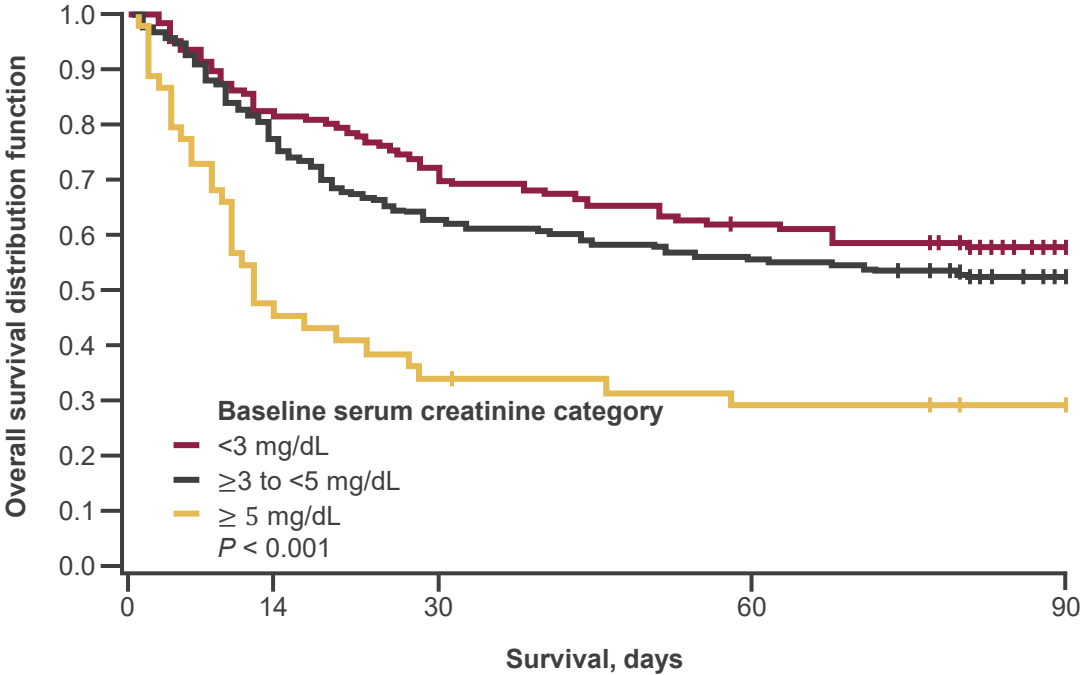
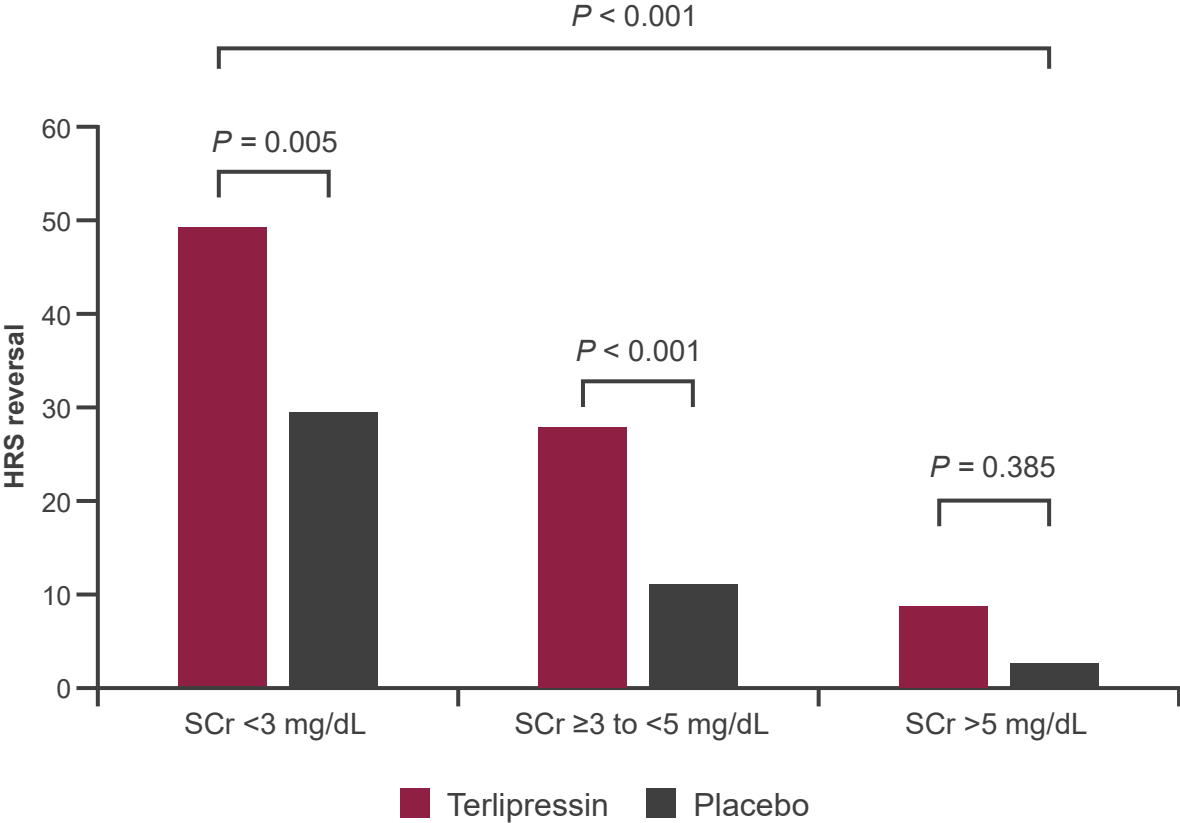


Achieving CHRSR With Terlipressin Improves Survival



Early Treatment is Associated With Higher HRS Reversal Rates

Pooled data from three phase 3 trials of terlipressin: integrated ITT population



Limitation of Use: Patients with SCr >5 mg/dL are unlikely to experience benefit.

AKI in ACLF: Renal Replacement Therapy

Intermittant vs Continuous RRT?

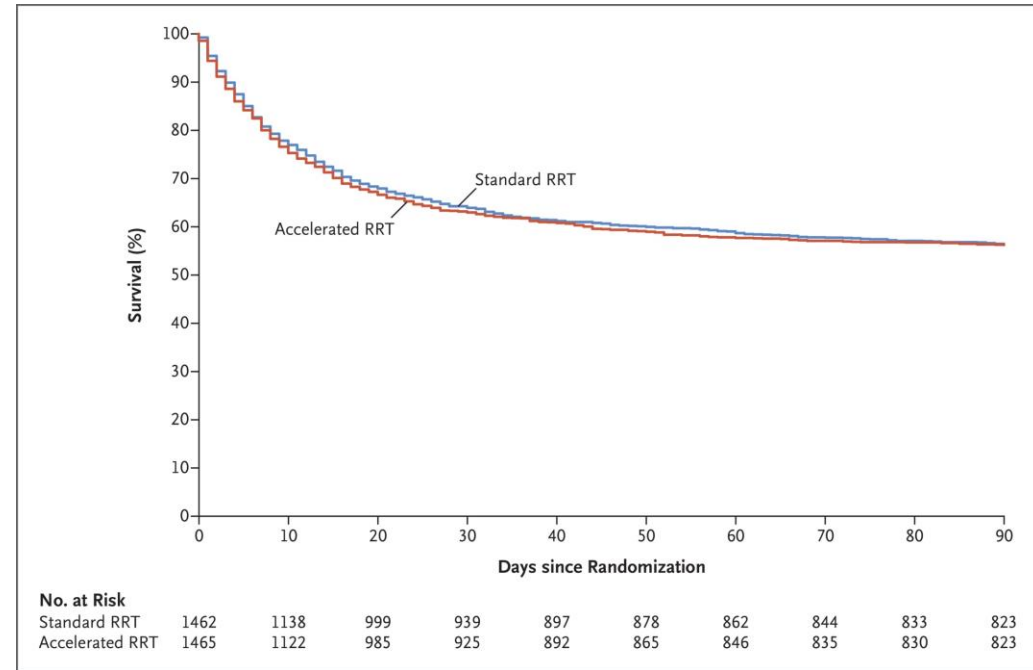
- CRRT likely safer¹ given BP issues in HRS

When? Accelerated vs Standard

- No difference KDIGO Stage 2 vs Stage 3²

Circuit anticoagulation?

- Start with no anticoagulation
- Citrate likely safe for short duration
- Heparin? Prostacyclin?



	Number of patients available for analysis				OR or MD Overlap weighting (95% CI)	p value
	CRRT	IHD	CRRT	IHD		
Primary outcome						
Death or RRT dependence at 90-days, n (%)	1590	606	823 (51.8)	329 (54.3)	0.81 (0.66 to 0.99)	0.044

**Death or RRT dependence
CRRT vs IHD: 51.8 vs 54.3%, p=0.044**

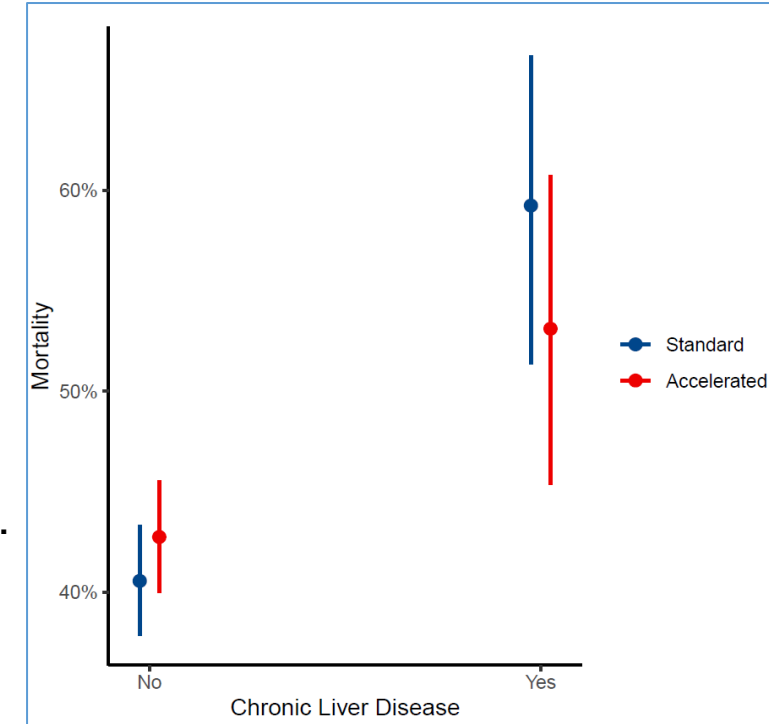
Initiation of RRT in critically ill patients with cirrhosis/CLD: Secondary analysis of STARRT-AKI

STARRT-AKI

- Critically-ill patients with AKI randomized to accelerated strategy (RRT within 12 hours after the patient had met eligibility criteria) or a standard strategy

Secondary analysis

- Patients with cirrhosis/CLD (n=337) vs those without CLD (n=2590)
- Cirrhosis/CLD pts: higher SOFA scores (13 vs. 12; $p < 0.001$) at enrollment.
- Most common initial modality CRRT in both groups (59% vs 54%; $p = 0.3$).**
- 90-day mortality higher (56% vs. 42%, $p < 0.001$) in CLD/cirrhosis group
- Days alive and free of RRT fewer in CLD/cirrhosis patients ($p < 0.001$).
- Accelerated strategy not associated with differences in mortality (OR 1.01; $p = 0.51$)
- No significant interaction between CLD versus non-CLD patients ($p = 0.16$ for interaction).



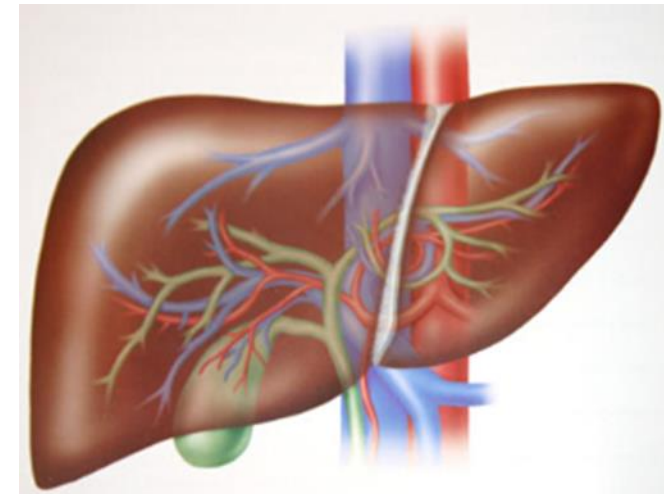
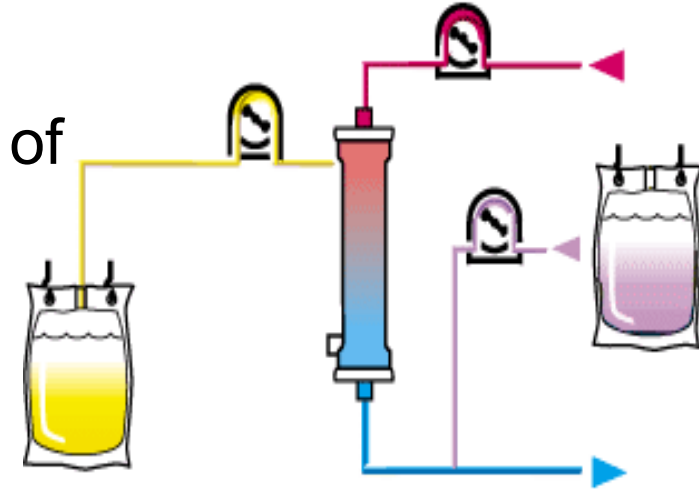
CRRT in critically-ill patients with cirrhosis/ACLF: CRRTnet

<u>Analysis 1</u>	All Cohort n = 1541	Liver n=250	Non-liver n=1291	p-value
Age (years, mean $\pm$ SD)	60 [50 - 69]	57 [49 - 63]	61 [51 - 70]	<0.001
SOFA score , median [IQR]	15 [12 - 17]	16 [13 - 18]	14 [12 - 16]	<0.001
ICU Length of Stay , days, median [IQR]	10 [4 - 20]	8 [3 - 14]	10 [4 - 21]	<0.001
Time (hours): ICU admission to CRRT initiation	27.2 [10.5 -73.8]	21.6[8.2 -48.9]	29.2 [11.0 - 77.4]	<0.001
Anticoagulation type , n (%)	(1262)	(187)	(1075)	<0.001
<i>Citrate</i>	710 (52.0)	87 (41.8)	623 (53.9)	
<i>Heparin</i>	95 (7.0)	7(3.3)	88 (7.6)	
<i>No anticoagulation</i>	442 (47.7)	93 (44.7)	349 (30.2)	
CRRT modality				0.34
<i>Continuous venovenous hemofiltration</i>	15.0%	16.9%	14.6%	
<i>Continuous venovenous hemodiafiltration</i>	84.6%	82.6%	85.0%	
<i>Other</i>	0.4%	0.5%	0.4%	
Survival at hospital discharge	46.9%	37.7%	48.7%	0.009
<u>Analysis 2</u>	Liver Cohort n = 250	Alive n=89	Deceased n=161	p-value
SOFA score , median [IQR]	16 [13 - 18]	14 [13 - 16]	17 [14 - 19]	0.003
ICU Length of Stay , days, median [IQR]	8 [3 - 14]	11 [8 - 20]	5 [2 - 10.5]	<0.001
CRRT duration , days, median [IQR]	3 [1 - 8]	5 [3 - 9]	3 [1 - 7]	<0.001
Received any intermittent hemodialysis (%)	55.9%	67.0%	24.1%	<0.001



Intraoperative CRRT : Physiologic derangements during LT

- Lactic acidosis: Clamping of large vessels (anhepatic phase)
- Hyperkalemia: reperfusion of the donor liver/graft and release of IVC cross clamp
- Hemodynamic instability/coagulopathy/fluid shifts
 - Blood product transfusions, crystalloid resuscitation
- Hyponatremia before transplant and abrupt correction during reperfusion



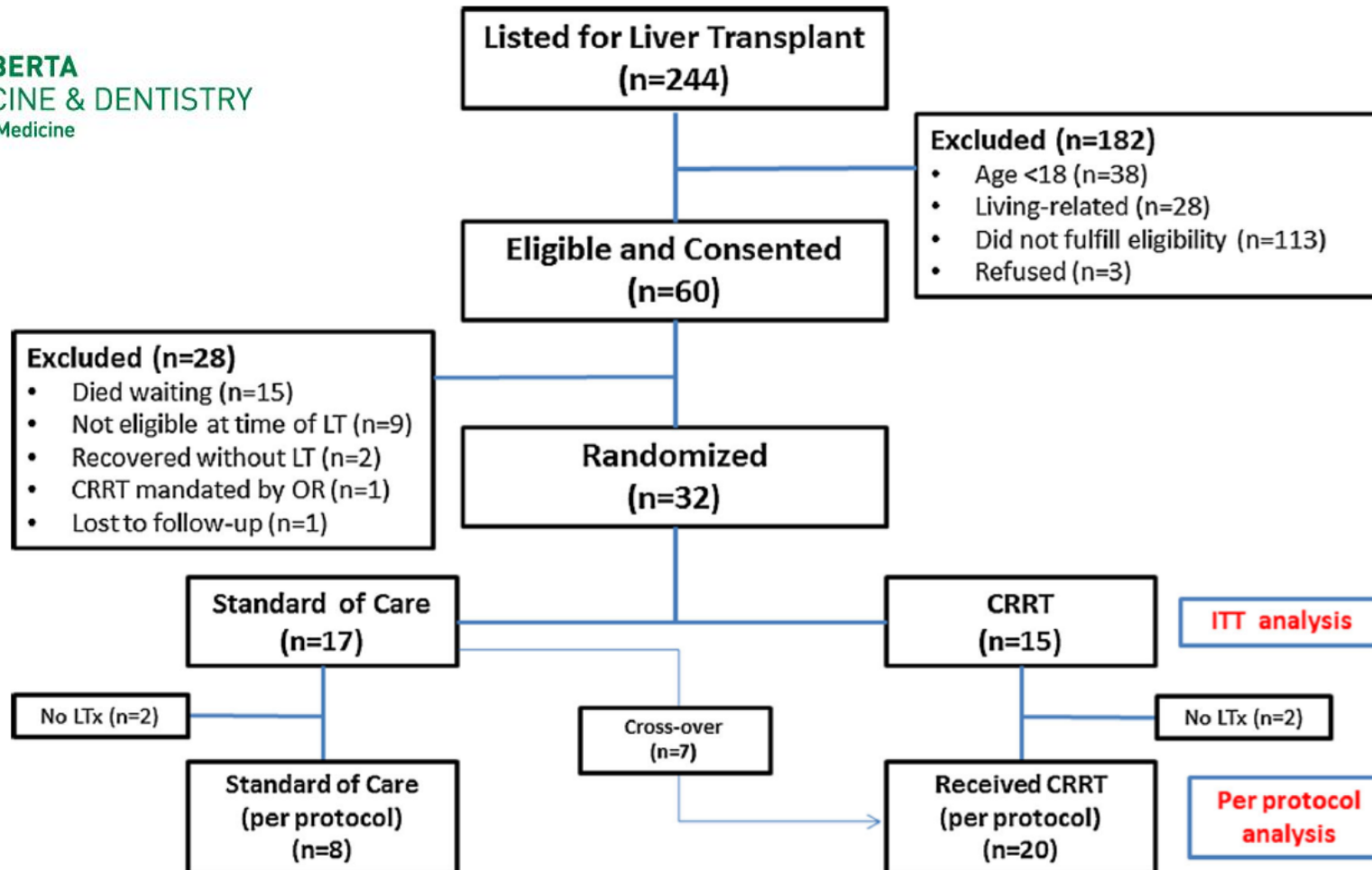


Fig. 1 Consort Diagram: Flow of screening, enrolment, and randomization for patients in the INCEPTION study. Intention-to-treat: 17 patients received standard of care, 15 patients received

intraoperative CRRT (IoCRRT). Per-protocol analysis: Of 28 patients who received liver transplantation after randomization, eight patients received standard of care, and 20 patients received IoCRRT

Post-LT Outcomes (per protocol n=28)

	All patients (n=28)	SOC (n=8)	IoCRRT (n=20)	P-value
RRT post-LT				
Post-operative RRT	18/28	4/8	14/20	0.25
RRT ICU discharge	2/28	1/8	1/20	0.65
Survival post-LT				
30 days	27/28	8/8	19/20	1.0
1-year	23/25	7/7	16/18	0.64
Dialysis dependence				
30 days	2/27	0/8	2/19	0.50
1 year	1/22	0/5	1/17	0.37
Creatinine (umol/L)				
30 days	123 (79-145)	113 (73-153)	127 (79-142)	0.99
180 days	120 (89-145)	136 (120-170)	105 (77-133)	0.034

Pre-operative vs Intraoperative CRRT for Liver Transplant

HUANG ET AL.

LIVER TRANSPLANTATION, August 2020

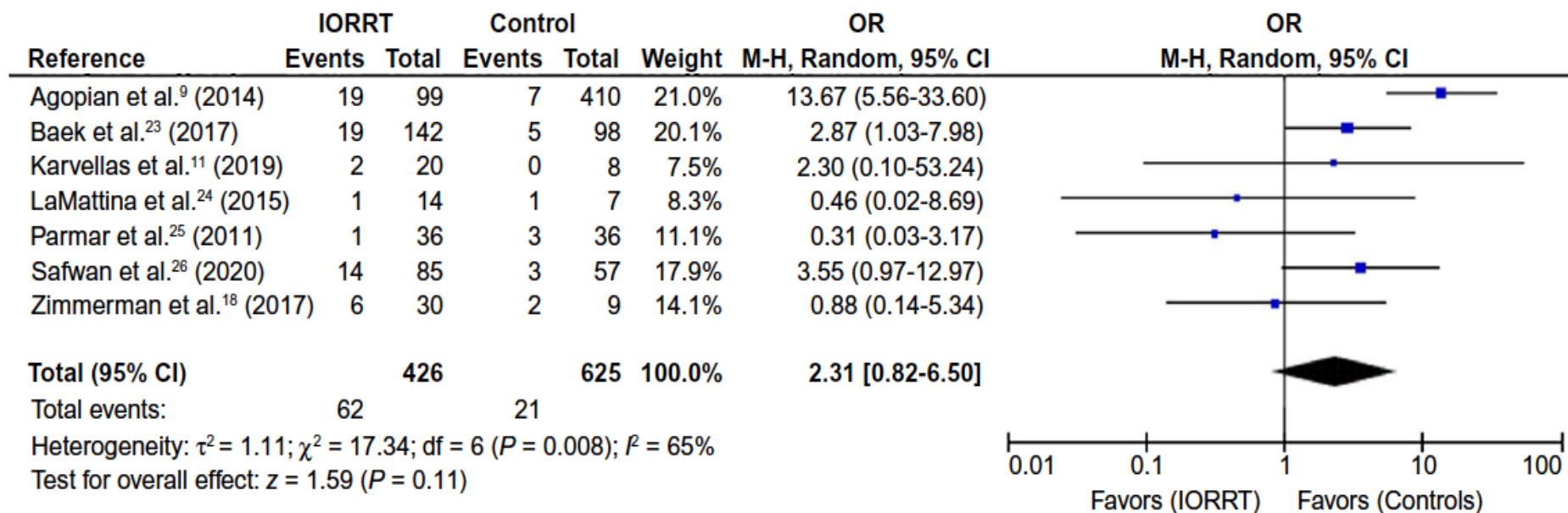


FIG. 2. Forest plot of the short-term mortality rates between LT patients with or without IORRT.

Challenging to study loCRRT:
Consider in patients with oliguric AKI (pre-operative RRT in others?)



Simultaneous Liver–Kidney Allocation Policy: A Proposal to Optimize Appropriate Utilization of Scarce Resources

R. N. Formica^{1,*}, M. Aeder², G. Boyle³,
A. Kucheryavaya³, D. Stewart³, R. Hirose⁴ and
D. Mulligan¹

UNOS criteria*

1. AKI requiring RRT for > 6 (consecutive) weeks
2. Measured/calculated GFR < 25ml/min for 6 weeks.
3. Any combination 1) and 2) for 6 weeks

Challenges

- Lack of robust data
- Prioritizing combined SLK recipients over young high priority renal candidates
- Simultaneous vs. sequential
 - Immunosensitization
 - Operative risk

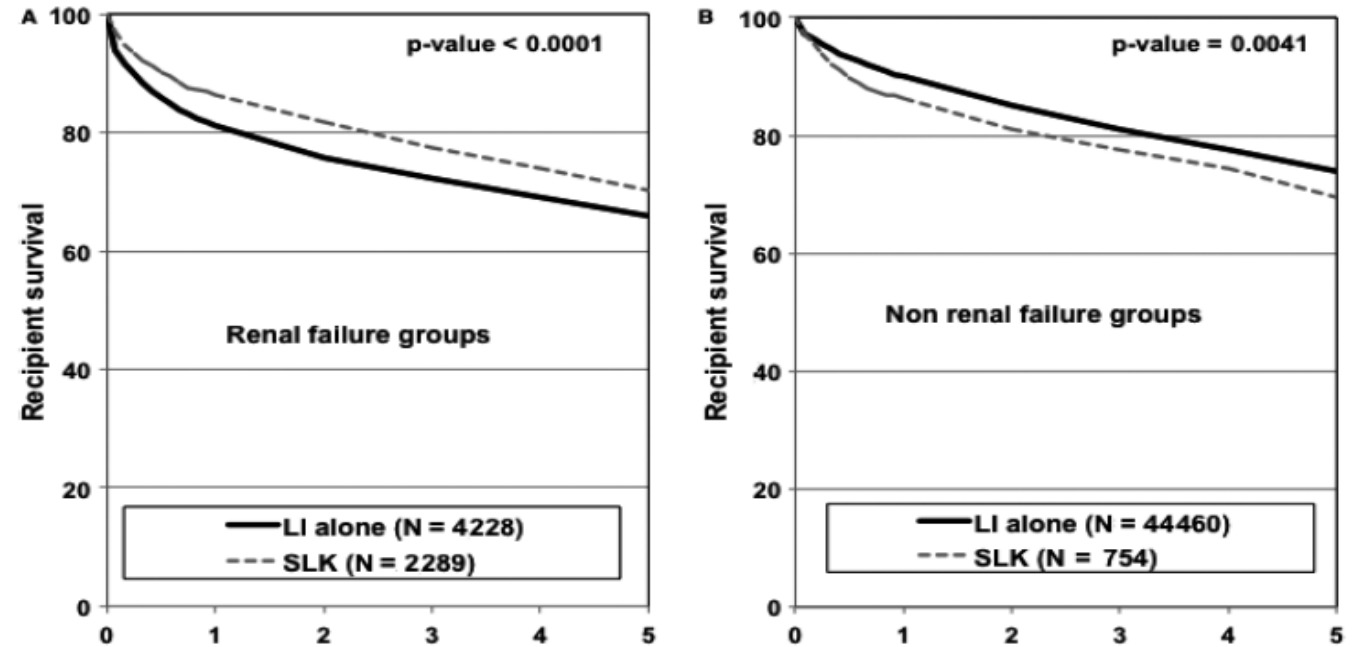
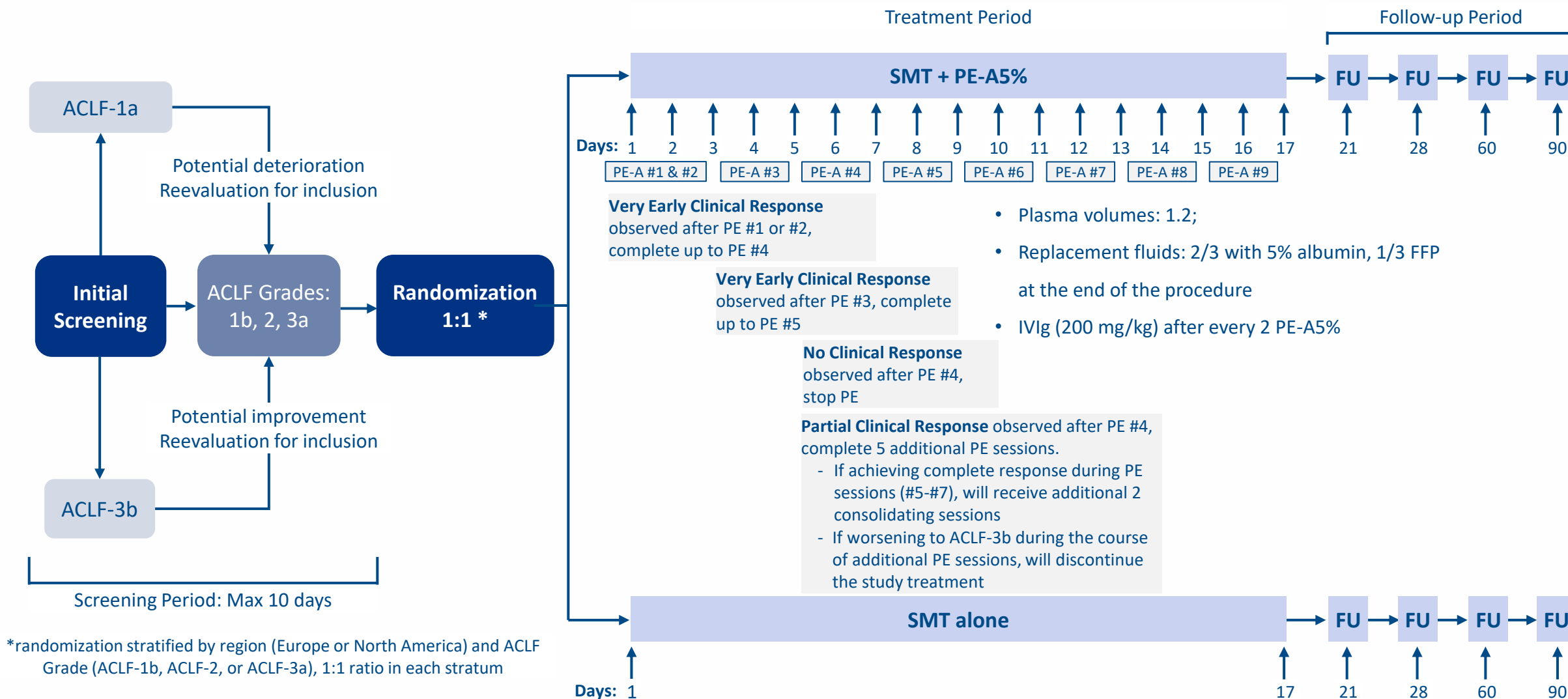


Figure 3: Unadjusted survival advantage of receiving SLK versus LI (March 1, 2002 to December 31, 2012). (A) Survival of SLK versus LI for patients with renal renal failure defined as ≥ 2 mo of dialysis or estimated GFR ≤ 25 mL/min. (B) Survival of SLK versus LI for patients not meeting the definition of renal failure. LI, liver alone; SLK, simultaneous liver–kidney.

- RF ~ ≥ 2 months RRT or GFR ≤ 25 ml/min
- Non RF ~ not meeting above definition of RF



Short-term Survival of Subjects With Acute-on-chronic Liver Failure After Plasma Exchange With Human Serum Albumin 5% (APACHE Trial)



*randomization stratified by region (Europe or North America) and ACLF Grade (ACLF-1b, ACLF-2, or ACLF-3a), 1:1 ratio in each stratum

ACLF = Acute-on-chronic liver failure; FFP = Fresh frozen plasma; FU = Follow-up visit; IVIg = intravenous immunoglobulin; PE-A5% = Plasma exchange albumin 5%; SMT = Standard medical treatment

Demographic and Baseline Characteristics - ITT Population

Characteristics	SMT+PE-A5% (N=135)	SMT (N=139)	Total (N=274)
Age, years, mean (SD)	50.3 (10.9)	51.1 (11.4)	50.7 (11.2)
Sex, n (%)			
Male	89 (65.9)	97 (69.8)	186 (67.9)
Female	46 (34.1)	42 (30.2)	88 (32.1)
Weight, kg, mean (SD) ^[1]	88.2 (21.9)	87.9 (23.5)	88.0 (22.7)
Race, n (%) ^[2]			
White	121 (89.6)	118 (84.9)	239 (87.2)
Black or African American	7 (5.2)	12 (8.6)	19 (6.9)
Asian	0	4 (2.9)	4 (1.5)
American Indian or Alaskan Native	1 (0.7)	0	1 (0.4)
ACLF Grade at Randomization, n (%)			
ACLF-1b	28 (20.7)	31 (22.3)	59 (21.5)
ACLF-2	77 (57.0)	75 (54.0)	152 (55.5)
ACLF-3a	30 (22.2)	33 (23.7)	63 (23.0)
Organ Support at Baseline, n (%)			
Vasopressors	11 (8.1)	23 (16.5)	34 (12.4)
Mechanical ventilation	5 (3.7)	7 (5.0)	12 (4.4)
Renal replacement therapy	15 (11.1)	16 (11.5)	31 (11.3)
CLIF-C ACLF Score at Baseline, mean (SD) ^[3]	51.0 (7.3)	51.7 (8.1)	51.4 (7.7)

[1] n=127, SMT+PE-A5%; n=138, SMT. [2] Participants may have been counted in more than one category. [3] n=128, SMT+PE-A5%; n=138, SMT

Baseline is defined as the last non-missing measurement taken prior to the first PE session start date/time for SMT + PE-A 5% participants and the last non-missing measurement taken on or prior to randomization date for SMT participants.

ACLF = Acute-on-chronic liver failure; ITT = intent-to-treat; PE-A5% = Plasma exchange albumin 5%; SD = Standard deviation; SMT = standard medical treatment

Efficacy exploratory subgroup: 90-day overall survival without prior liver transplant by ACLF groups

Endpoint Measure	Subgroup category	SMT+PE-A5% N = 135; n (%) ^[1]	SMT N= 139 n (%) ^[1]	Hazard Ratio [95% CI] ^[2]
Percent of participants with death through 90 days after randomization without prior liver transplant	ACLF-1b	6 (21.4)	10 (32.3)	0.73 [0.27, 2.02]
	ACLF-2	28 (36.4)	39 (52.0)	0.55 [0.34, 0.90]
	ACLF-3a	17 (56.7)	20 (60.6)	0.83 [0.43, 1.59]

The primary efficacy endpoint was met and showed significantly increased 90-day overall survival in the SMT+PE-A5% group as compared to the SMT group. This effect was mainly observed in patients with less severe forms of ACLF (1b and 2)

[1] Percentage of [participants with an event up to the analysis cut-off Day, n] / [number of participants in the ITT group, N].

[2] HR [95% CI] from a stratified Cox PH model; stratification factor included was the region (EU or NA).

ACLF = Acute-on-chronic liver failure; CI = Confidence Interval; ITT = Intent-to-Treat; PE-A5% = Plasma exchange albumin 5%; SMT = standard medical treatment

CLIF-C ACLF Score on Admission is a Predictor of Mortality in Critically-Ill Cirrhotic Patients

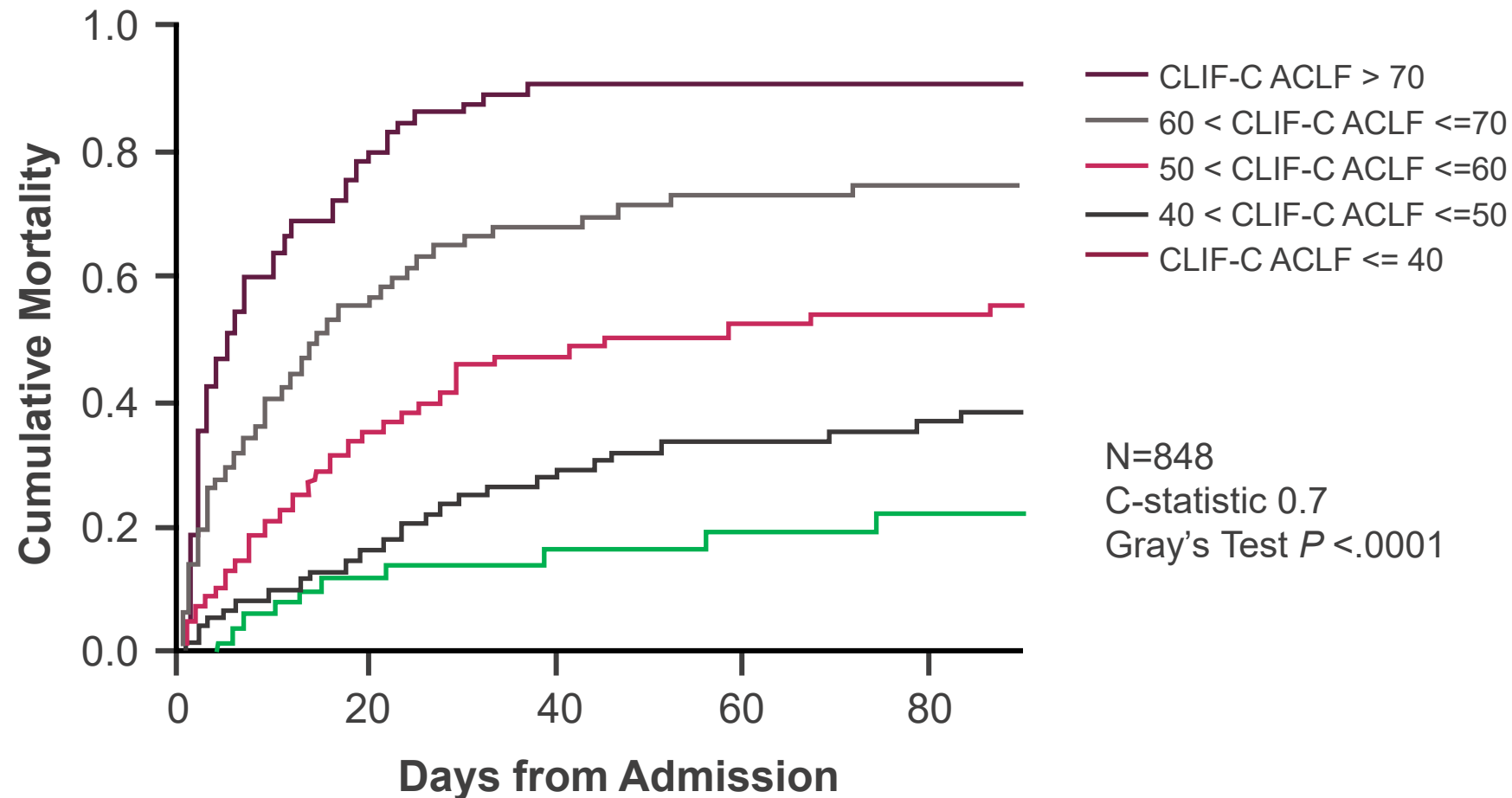


Figure:
Cumulative
incidence function
(mortality)
stratified by CLIF-C
ACLF score (0-100)
on admission

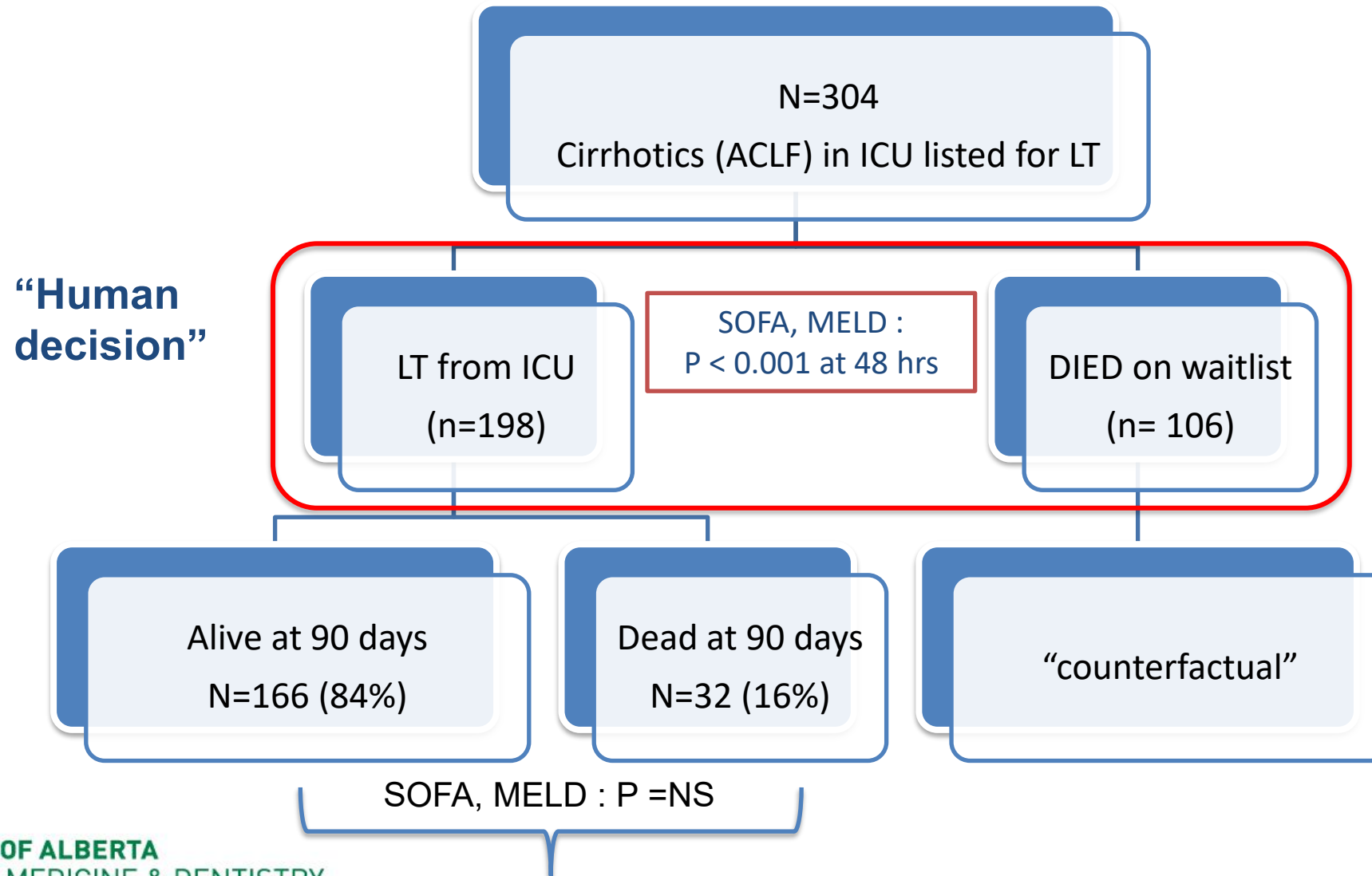
Dynamic Prognostication in Critically Ill Cirrhotic Patients with Multiorgan Failure in ICUs

ACLF Can Be Dynamic: Day 3

	ACLF Grade Admission	ACLF Grade Day 3	28-day Mortality	90-day Mortality
No ACLF		82 (20%)	6/82 (7%)	10/82 (12%)
Grade 1	82/419 (20%)	76 (18%)	10/76 (13%)	17/76 (22%)
Grade 2	159/419 (38%)	110 (26%)	37/110 (34%)	52/110 (47%)
Grade 3	178/419 (42%)	151 (36%)	105/151 (70%)	121/151 (80%)
	N=419	N=419	* $P < 0.0001$	* $P < 0.0001$

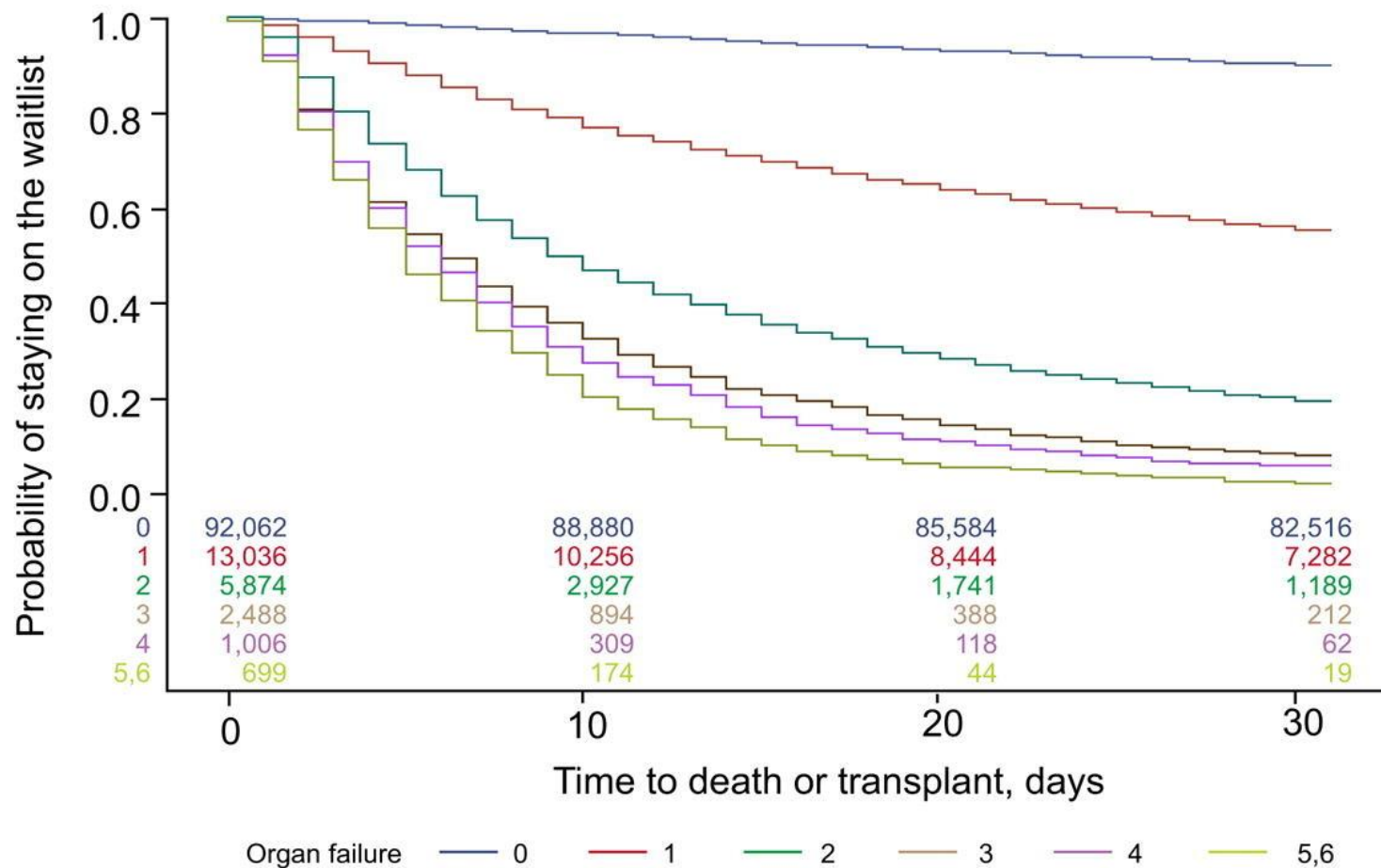
- 167/419 (40%) improved by at least one ACLF grade
- 200/419 (48%) no change
- 52/419 (12%) deteriorated by at least one ACLF grade
- Mortality correlated with grade on day 3*

Liver transplantation in the critically ill: a multicenter Canadian retrospective cohort study



LT in cirrhosis/ACLF patients: UNOS

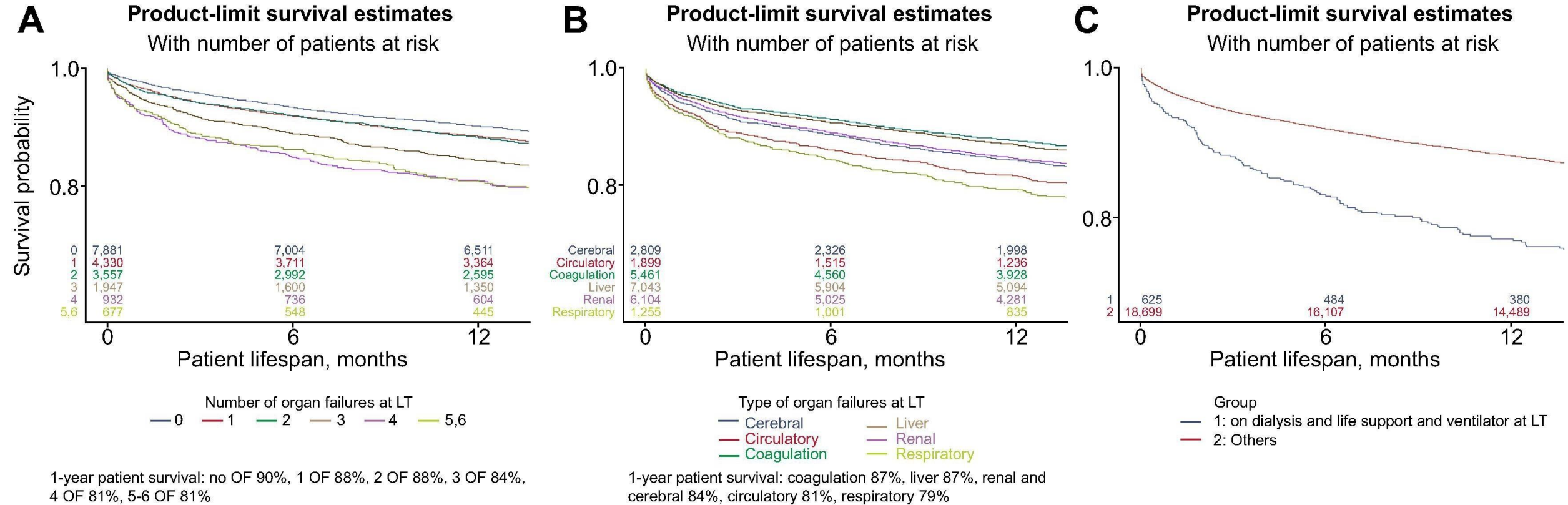
Probability of staying alive on the waiting list for more than 30 days without transplantation stratified by the number of organ failures



30 day removal from the list because of death or LT: no OF 10%, 1 OF 45%, 2 OF 80%, 3 OF 92%, 4 OF 94%, 5, 6 OF 98%

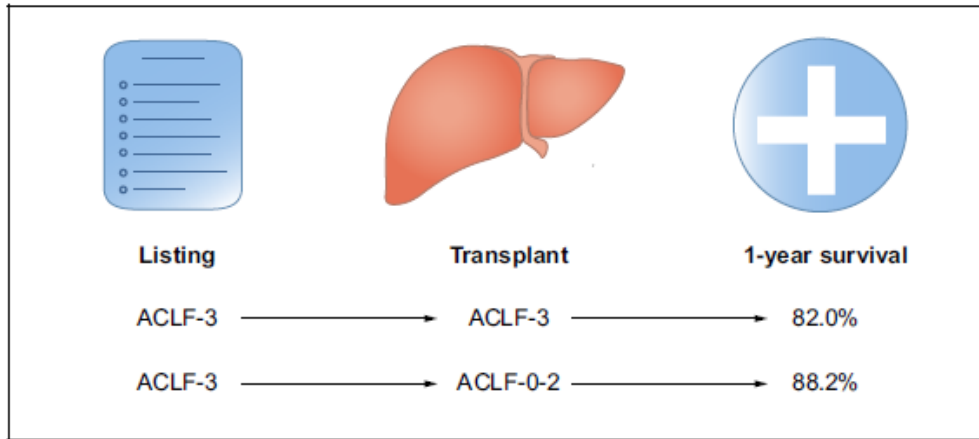


Liver transplantation in patients with multiple organ failures: Feasibility and outcomes



Effect of the clinical course of acute-on-chronic liver failure prior to liver transplantation on post-transplant survival[☆]

Vinay Sundaram^{1,*}, Shannon Kogachi¹, Robert J. Wong², Constantine J. Karvellas³, Brett E. Fortune⁴, Nadim Mahmud⁵, Josh Levitsky⁶, Robert S. Rahimi⁷, Rajiv Jalan⁸

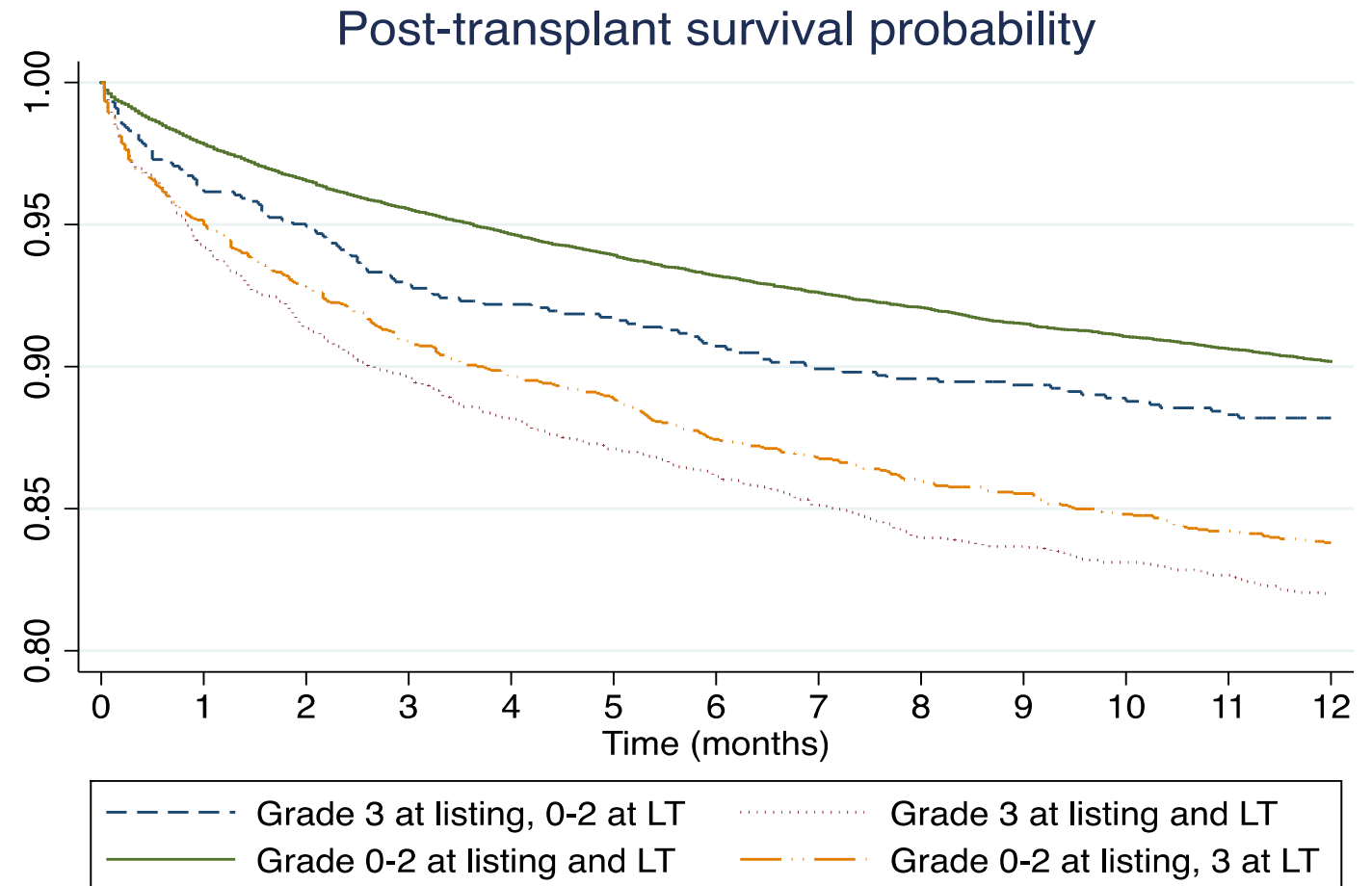


- Improvement in brain and circulatory failure and removal from mechanical ventilation are associated with post-LT survival.

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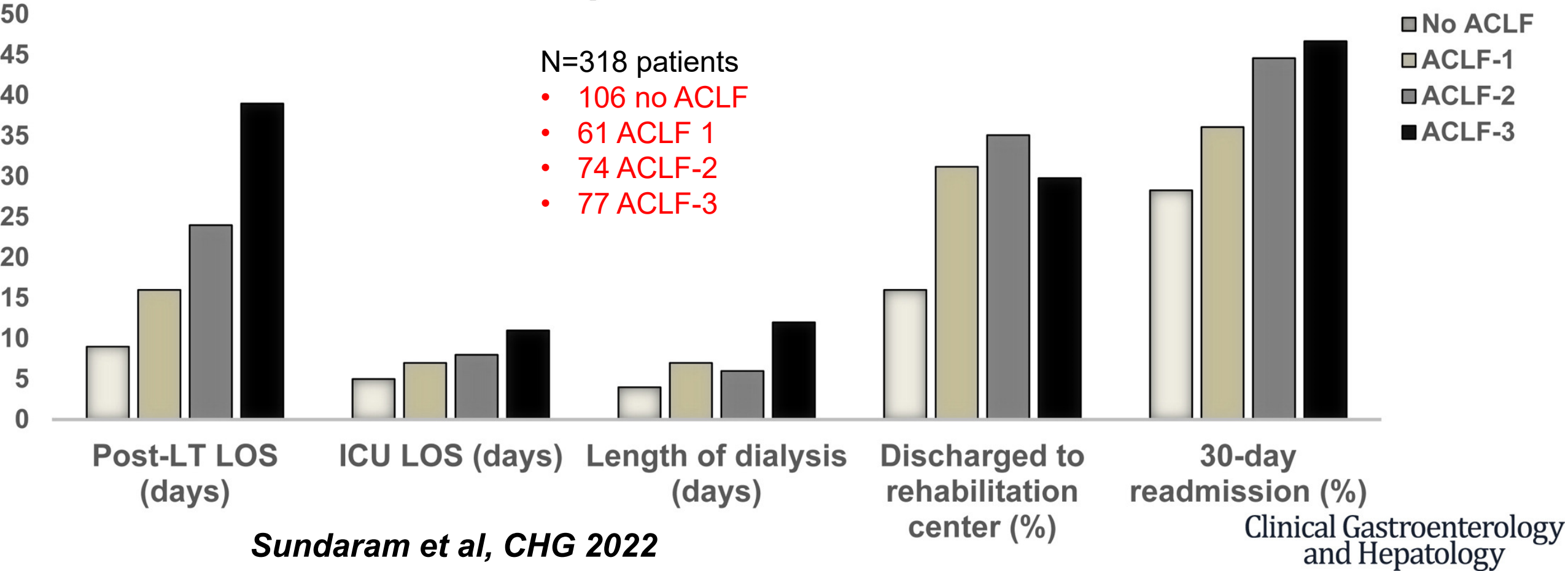


UNIVERSITY OF ALBERTA
FACULTY OF MEDICINE & DENTISTRY
Department of Critical Care Medicine



Patients With Acute-on-Chronic Liver Failure Have Greater Healthcare Resource Utilization After Liver Transplantation

Post-transplant healthcare resource utilization



Summary: Management of ACLF (1 of 2)

Acute on chronic liver failure: cirrhosis with multi-organ failure

Sepsis: Early appropriate antibiotics improves outcome in ACLF

Circulatory failure: Perform early baseline assessment of volume/perfusion status

- Best done with dynamic modalities (i.e. bedside echocardiography)
- Avoid fluid overload
- Norepinephrine is first line vasopressor

Respiratory failure: Lung protective strategy in ventilated patients

- Consider both liver and non-liver related causes of acute lung injury

Summary: Management of ACLF (2 of 2)

AKI: Vasoconstrictor therapies are associated with reversal of HRS-AKI

- *Responders to vasoconstrictor therapies have better outcomes*
- More studies required regarding optimal timing and modality (CVVH vs. CVVHDF) and other factors (circuit anticoagulation) in ACLF patients
- It is unclear if pre-emptive RRT/CRRT immediately prior to LT is non-inferior to intraoperative CRRT

Prognosis in ACLF: CLIF_ACLF (*absence of liver transplant*)

Futility with LT: Waitlist mortality is likely our best metric.

Consult ICU early for the ACLF patient who is *potentially transplantable*.



Practice Guidance



AASLD Practice Guidance on Acute-on-chronic liver failure and the management of critically ill patients with cirrhosis

Constantine J Karvellas* MD SM, Jasmohan S Bajaj MD MS, Patrick S Kamath MD, Jacqueline G O'Leary MD, Lena Napolitano MD, Elsa Solà MD, PhD, Ram Subramanian MD MBA, Florence Wong MD, Sumeet K Asrani MD MSc*

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UNIVERSITY OF ALBERTA
FACULTY OF MEDICINE & DENTISTRY
Department of Critical Care Medicine