Critical care in acute liver failure

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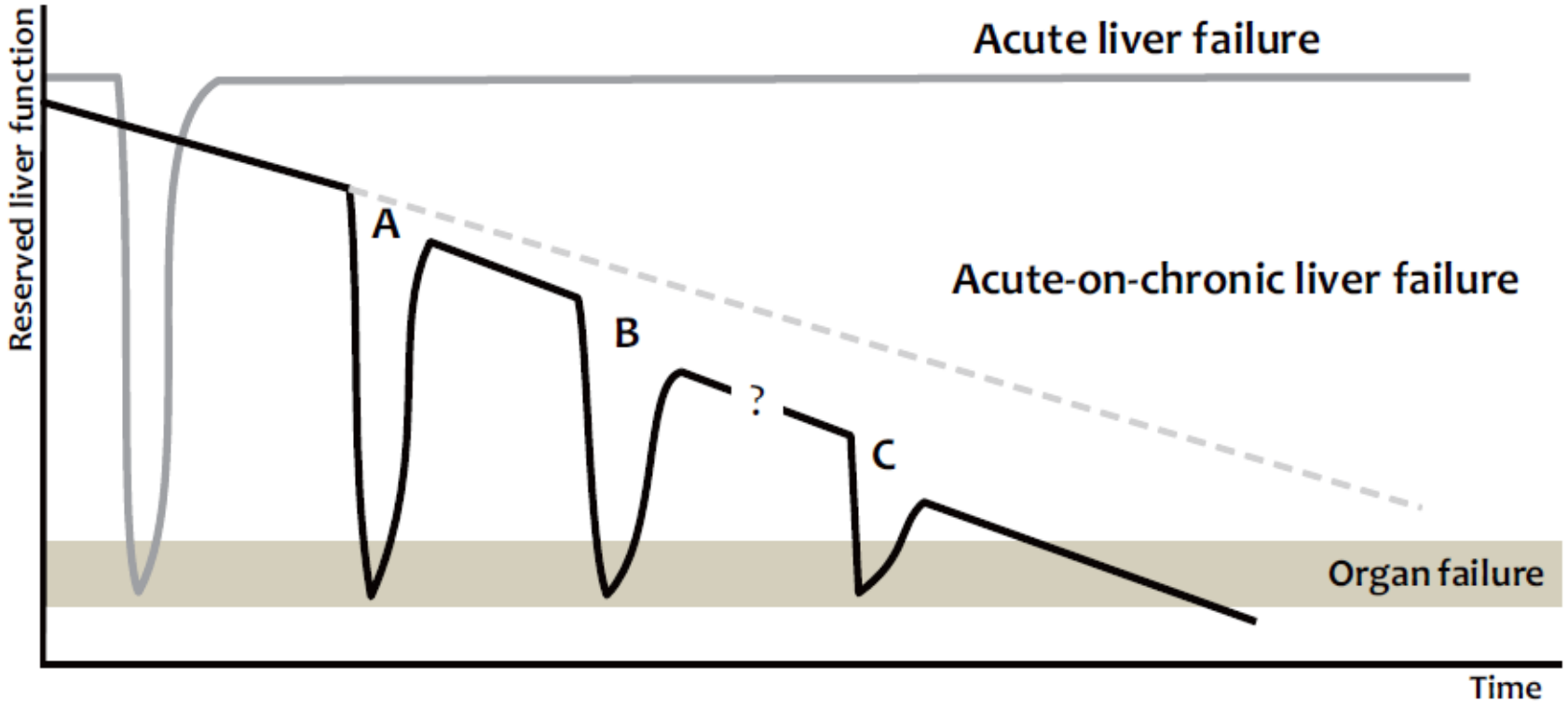
Today's content

- Definition and classification of liver failure
- Things to consider in acute liver failure
- Things to consider in acute on chronic liver failure

Liver failure: definition

- Inability of the liver to perform its normal synthetic and metabolic function as part of normal physiology.

Clinical spectrum



Kim TY et al., Clin Mol Hepatol 2013

Acute liver failure

- Acute loss of hepatocellular function
- Systemic inflammatory response
- Multi-organ system failure

- Evidence of **coagulation abnormality**, usually an INR ≥1.5, and any degree of mental alteration (**encephalopathy**) in a patient without preexisting cirrhosis and with an illness of < 26 weeks' duration

Prothrombin time (PT)

- Measures of the extrinsic pathway of coagulation.
- Time it takes plasma to clot after addition of tissue factor.
- The speed is greatly affected by levels of factor VII.
- **VII is synthesized in the liver**
- **Half-life is 3.5 hour**

Why encephalopathy?

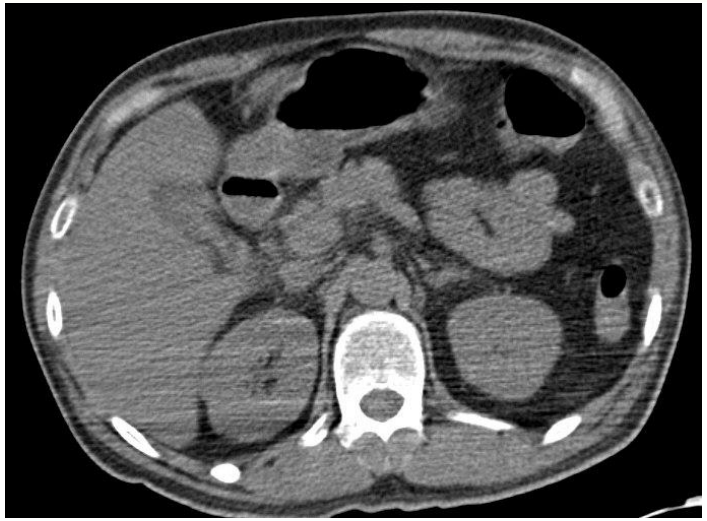
- The most serious **complication** of acute liver failure

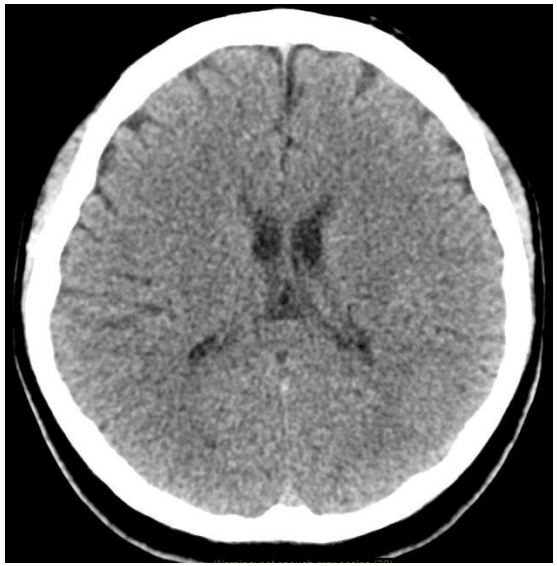
Case

- 42/M
- Heavy alcoholics (>100 g/d)
- URI symptoms for a weeks
- Sleeping tendency for 3-4 days
- **Drowsy mental status**
  - TB: 5.9 AST/ALT: 1123/2678 **PT INR: 5.75**
  - Brain CT: non specific
- Referred to ER

Case description

- Mental status: semicoma
- Icteric sclera
- LAB
  - TB: 10.2 AST/ALT: 351/1180
    BUN/Cr: 52.3/2.51 PT INR: 2.05
    → *Outside (TB: 5.9 AST/ALT: 1123/2678 PT INR: 5.75)*
  - ABGA: 7.51-34-54-26.8
  - Lactic acid: 6.7
  - Viral marker: HBsAg- HBsAb+, HBcIgG+, **HAV IgM+, HAV IgG+,** anti-HCV-





Clinical course

- HD 0
  - Emergent living donor evaluation: deferred → DDLT listing
- HD 1
  - Seizure developed → not controlled
- HD 2
  - Aggravated neurologic exam, pupil (4mm/4mm fix)
- HD 3
  - EEG (electrical inactivity) CT angiography (no intracranial arterial blood flow)
  - Brain death
- HD 7
  - Expired (multi-organ failure)

Most dangerous signal

- Cerebral edema and intracranial hypertension.

- Pathogenesis: multi-factorial
  - Osmotic disturbances in the brain
  - Heightened cerebral blood flow d/t loss of cerebrovascular autoregulation
  - Unknown

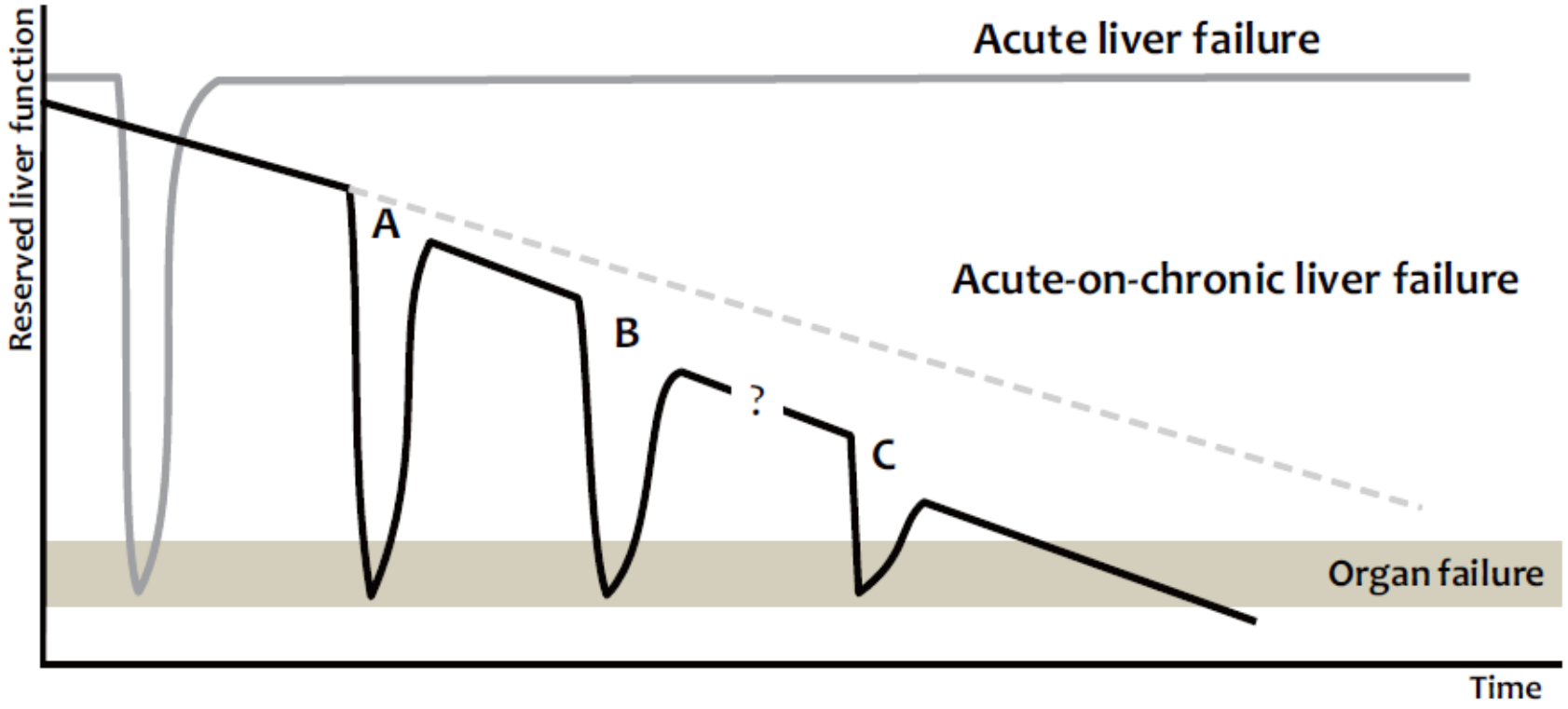
Summary

- Acute liver failure
  - **Coagulopathy**
  - **Encephalopathy**

TABLE 5. GRADES OF ENCEPHALOPATHY

GRADE	DEFINITION
I	Changes in behavior with minimal change in level of consciousness
II	Gross disorientation, drowsiness, possibly asterixis, inappropriate behavior
III	Marked confusion; incoherent speech, sleeping most of the time but arousable to vocal stimuli
IV	Comatose, unresponsive to pain, decorticate or decerebrate posturing

Clinical spectrum: ACLF



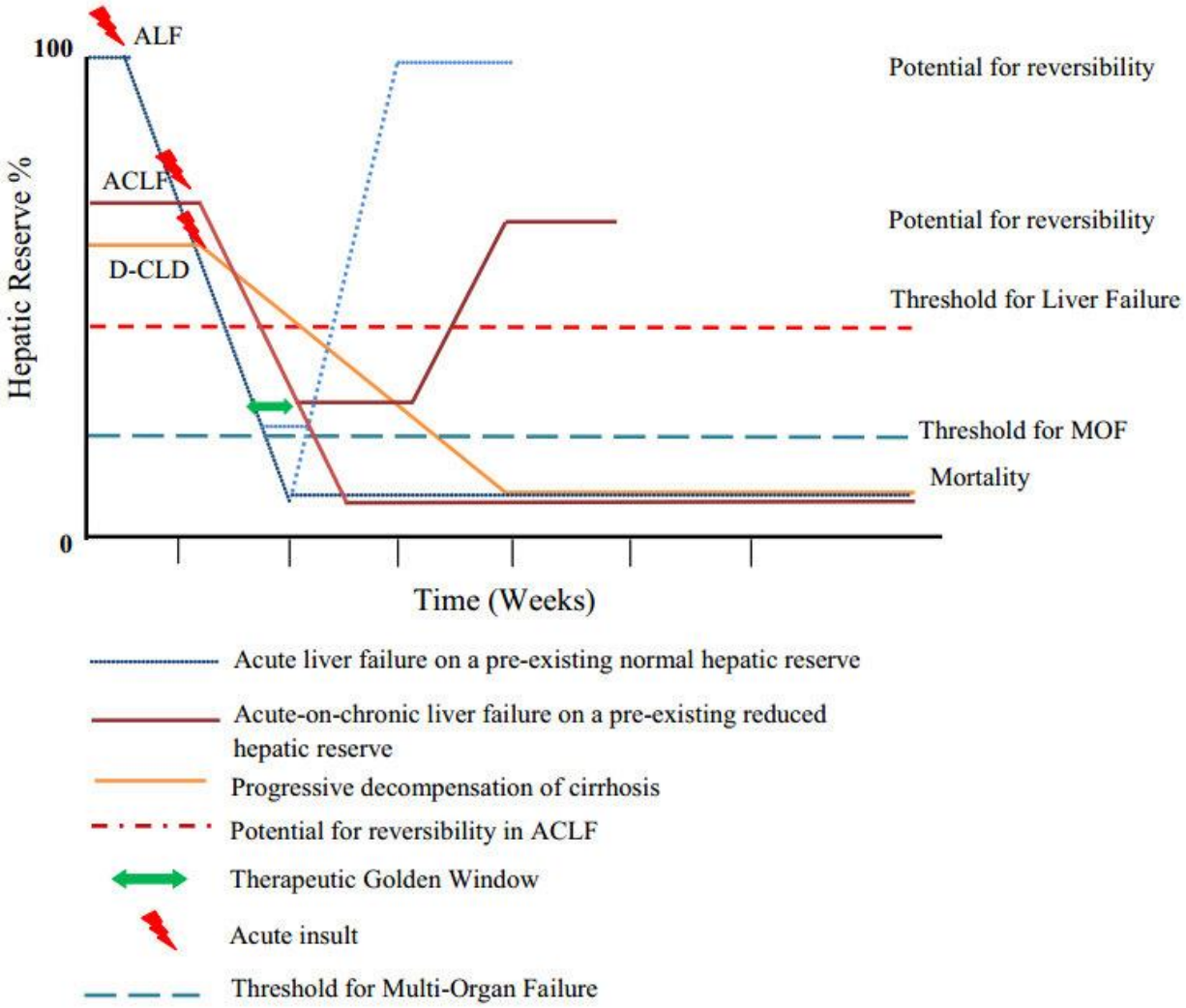
Kim TY et al., Clin Mol Hepatol 2013

ACLF

- No uniform definition present!
- Under hot debate!

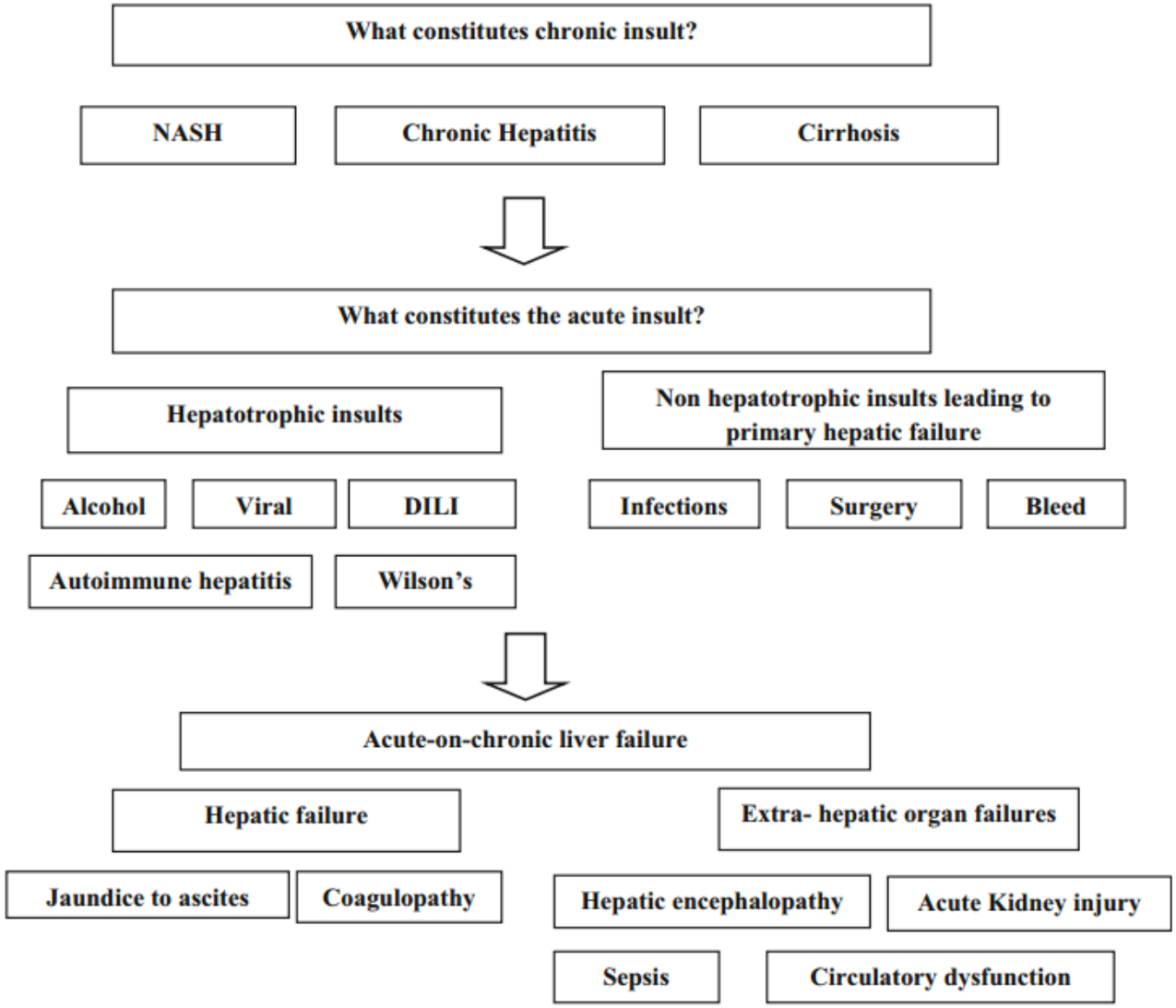
- West vs. East

ACLF concept



Sarin et al., Hepatol Int 2014;8:453

Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) 2014



APASL consensus definition

- The ACLF is an acute hepatic insult manifesting as **jaundice** (serum bilirubin :5 mg/dl) and **coagulopathy** (INR >1.5) complicated within 4 weeks by ***clinical ascites and/or encephalopathy*** in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and is associated with a high 28-day mortality.

EASL-CLIF definition (28d mortality >15%)

Table 1. CLIF-SOFA Score

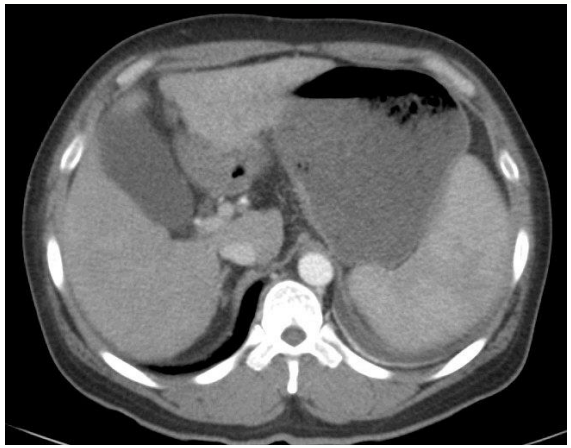
Organ/system	0	1	2	3	4
Liver (bilirubin, *mg/dL*)	<1.2	≥1.2 to ≤2.0	≥2.0 to <6.0	≥6.0 to <12.0	**≥12.0**
Kidney (creatinine, *mg/dL*)	<1.2	≥1.2 to <2.0	**≥2.0 to <3.5**	**≥3.5 to <5.0**	**≥5.0**
				or use of renal replacement therapy	
Cerebral (HE grade)	No HE	I	II	**III**	**IV**
Coagulation (international normalized ratio)	<1.1	≥1.1 to <1.25	≥1.25 to <1.5	≥1.5 to <2.5	**≥2.5 or platelet count ≤20×10^9/L**
Circulation (mean arterial pressure, *mm Hg*)	≥70	<70	**Dopamine ≤5 or dobutamine or terlipressin**	**Dopamine >5 or E ≤0.1 or NE ≤0.1**	**Dopamine >15 or E >0.1 or NE >0.1**
Lungs					
PaO_2/FiO_2 or	>400	>300 to ≤400	>200 to ≤300	**>100 to ≤200**	**≤100**
SpO_2/FiO_2	>512	>357 to ≤512	>214 to ≤357	**>89 to ≤214**	**≤89**

- ACLF grade 1.
  - Single kidney failure
  - Single cerebral failure + Cr 1.5 and 1.9 mg/dL.
  - Single failure of the liver, coagulation, circulation, or respiration + Cr 1.5 to 1.9 mg/dL and/or mild to moderate hepatic encephalopathy,
- ACLF grade 2: 2 organ failures
- ACLF grade 3: more than 3 organ failure

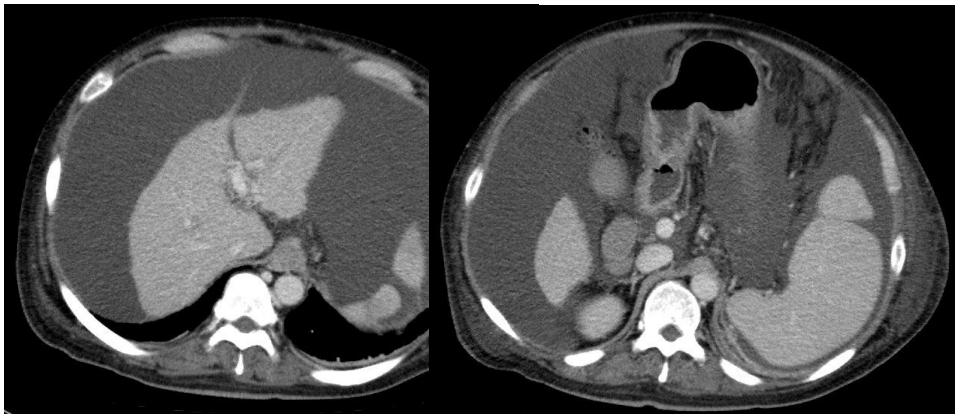
Case

- M/47
- Heavy alcoholics, known HBV (no tx history)
- Vibrio sepsis
  - Septic shock
  - Rt leg cellulitis → necrosis → fasciotomy
  - Renal failure with anuria → CRRT
- HBV DNA
  - HBV DNA 8600 IU/ml → entecavir start

Case

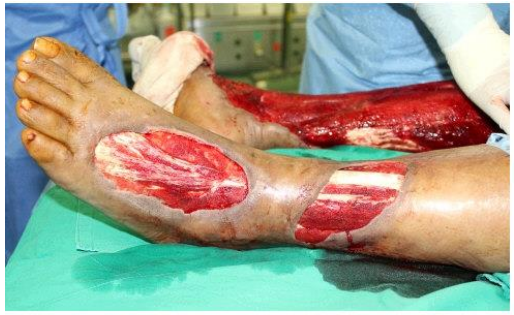


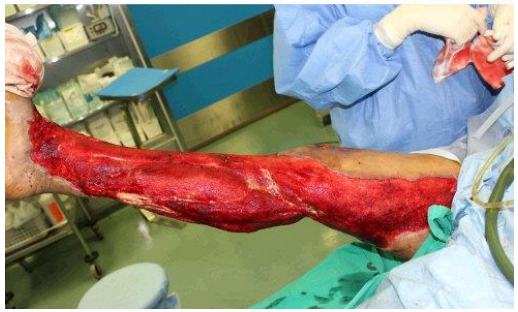
- Comatous metal status
- Lab
  - CBC: 12940 (90%)-11.2-62k
  - PT-INR: 2.2
  - Albumin: 3.4, Total bilirubin: 14.7, AST/ALT:49/27
  - BUN/Cr = 33.2/0.45 (on CRRT)



- ACLF type B (infection)

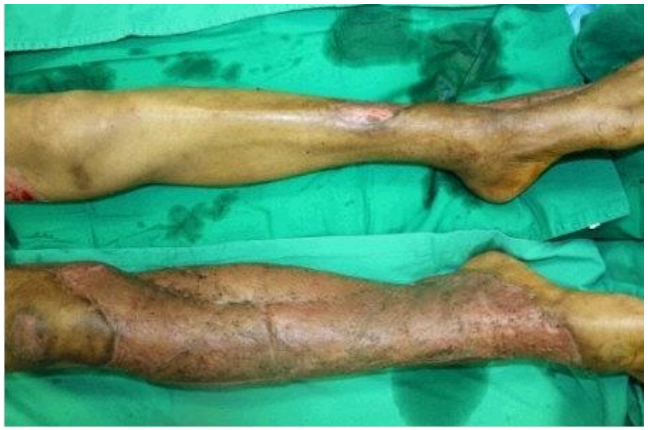
Hospital course (134 days, LT at HD 71)

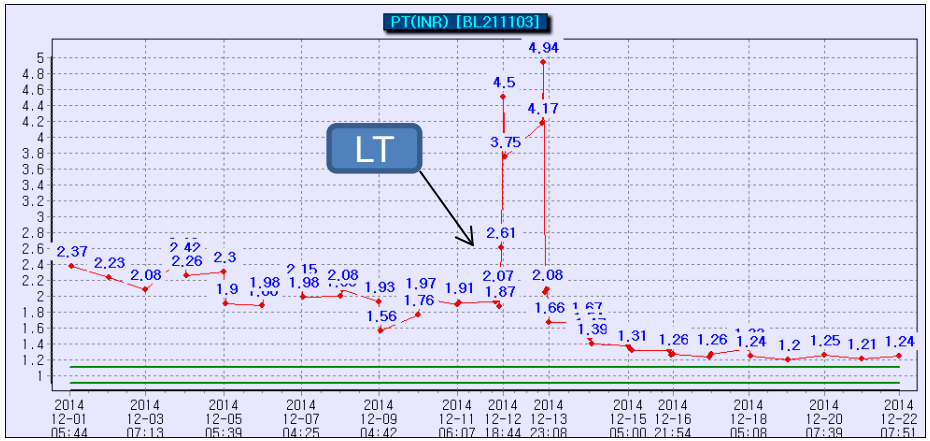


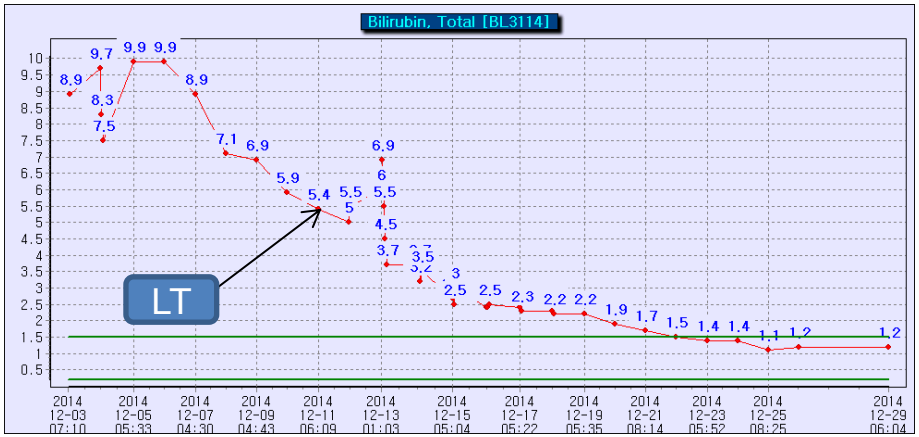


Infarcted regenerative nodules, S8 and S4 (4 nodules, up to 0.3x0.3x0.3 cm)

Micronodular cirrhosis, active with marked cholestasis and bile duct proliferation, clinically HBV-related







West vs. East

	EAST	WEST
Decompensated cirrhosis	No	Yes
Liver failure	Mandatory	Not mandatory
Non-hepatic insults (e.g., varix bleeding, infection)	Questionable	Yes

Decompensation: Varix bleeding, ascites, encephalopathy, Child-Pugh Class B

Case: LC-B, ascites → Pneumonia, complicated by renal failure (EAST: no!) (WEST: yes!)

World gastroenterology organization working party

- “ACLF is a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterized by acute hepatic decompensation resulting in **liver failure (jaundice and prolongation of the INR)** and **one or more extrahepatic organ failures** that is associated with increased mortality within a period of 28 days and up to 3 months from onset.”

Jalan R et al., Gastroenterology 2014;147:4

World gastroenterology organization working party

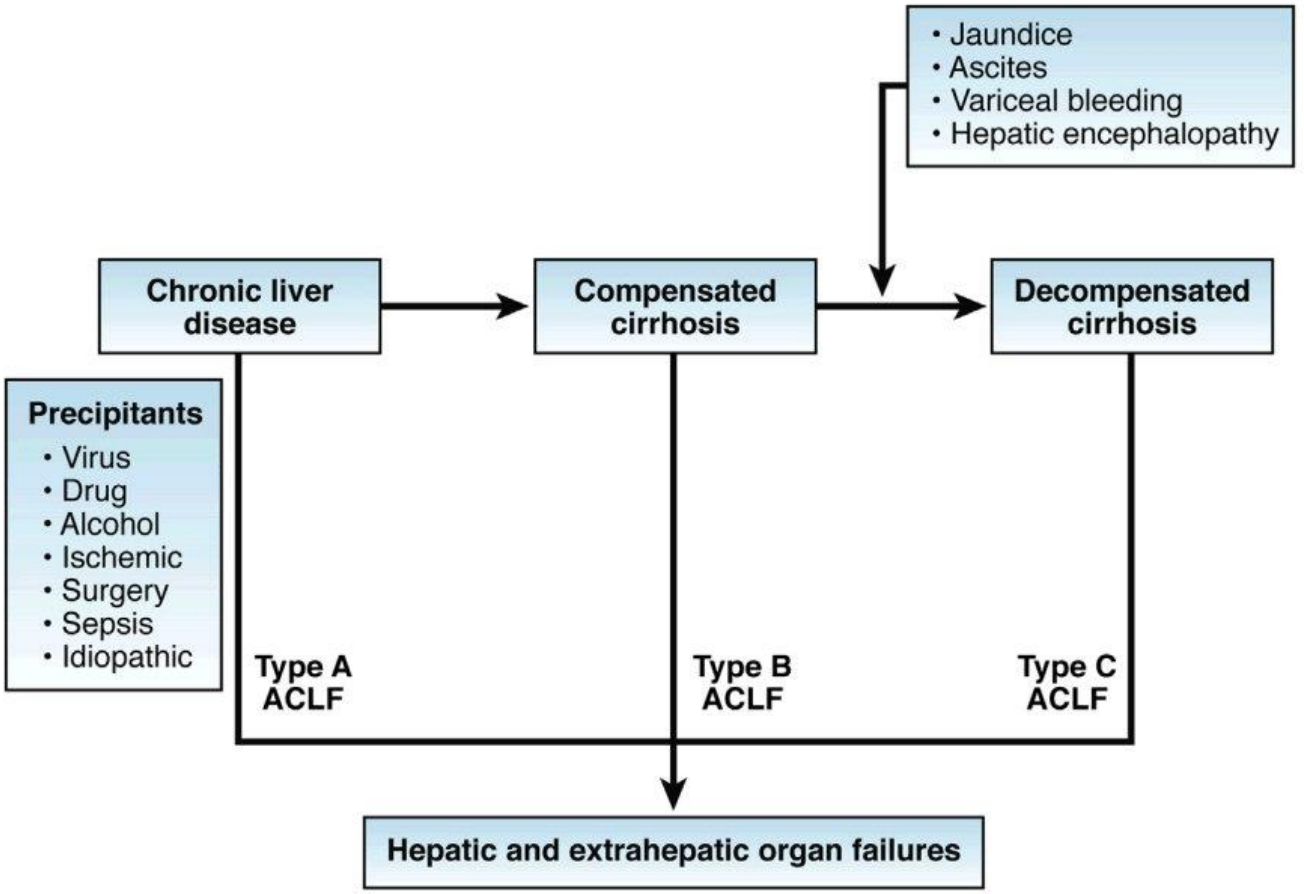
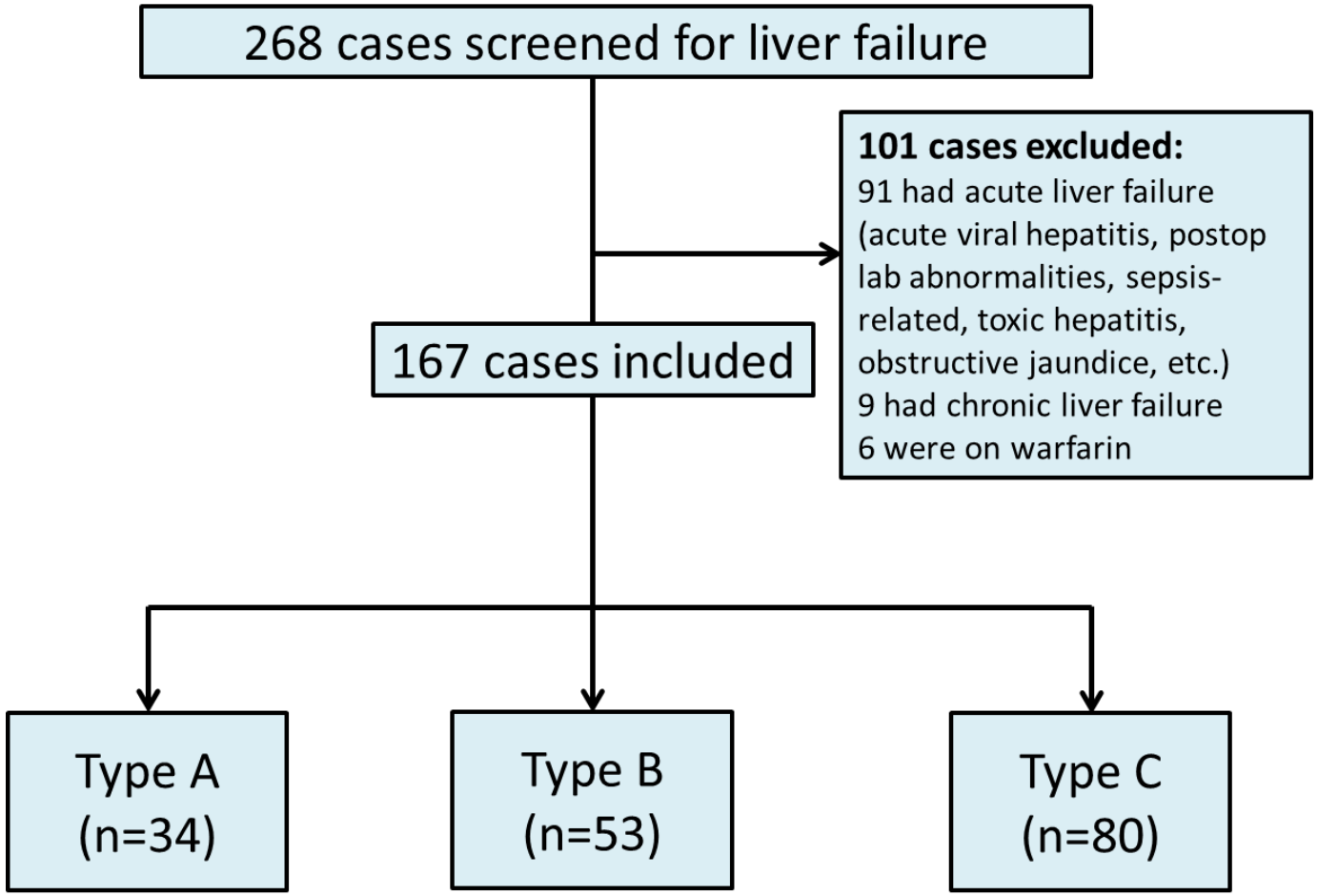


Figure 1. Proposed unifying pathogenesis for different types of acute-on-chronic liver failure (ACLF).

Jalan R et al., Gastroenterology 2014;147:4

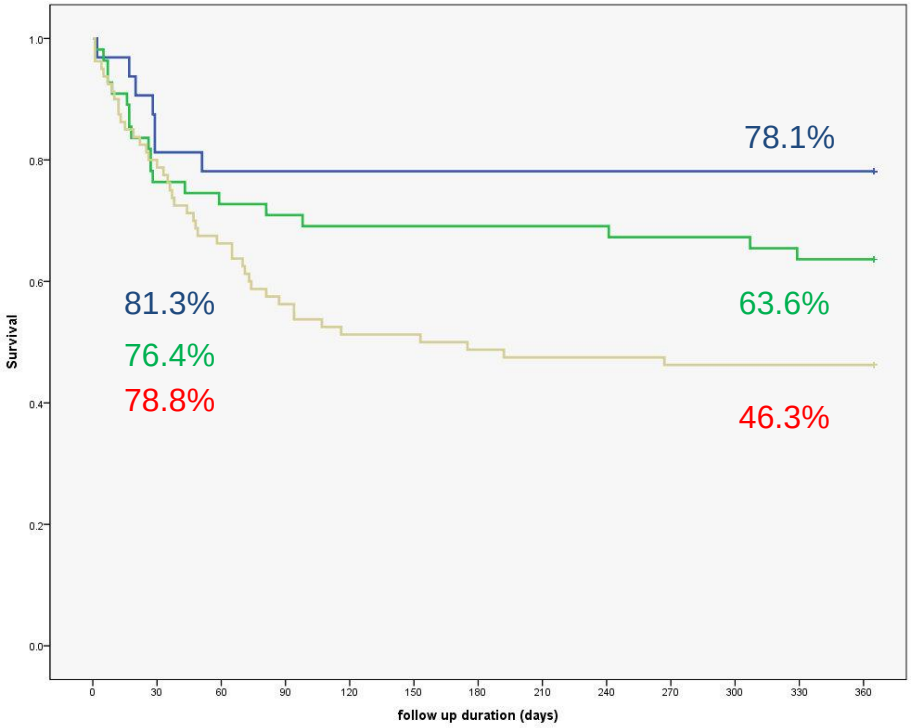
SMC data



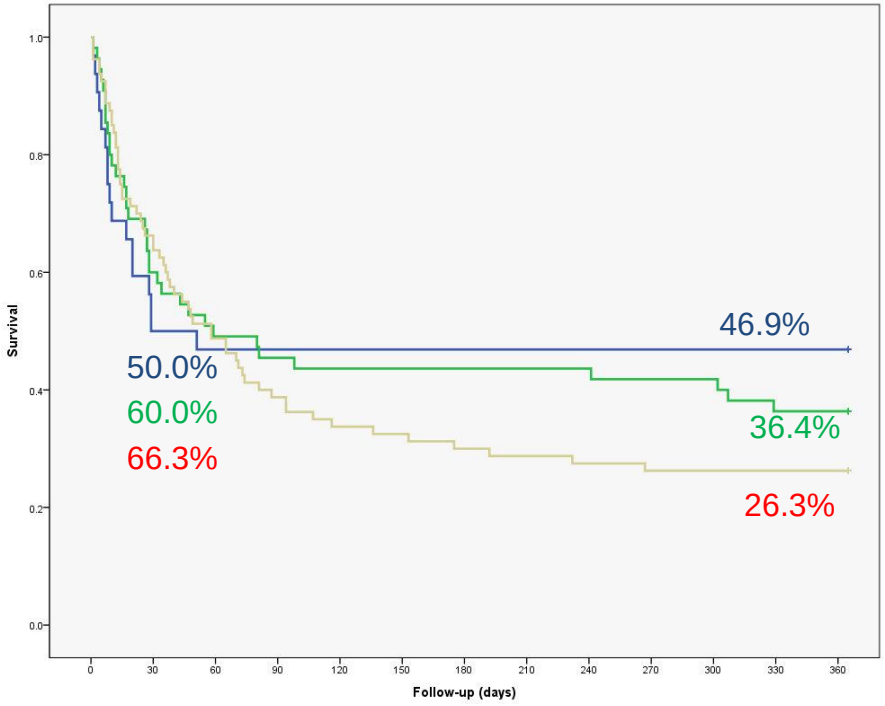
Hong YS et al., Intrim review

Survival by ACLF types

Overall survival



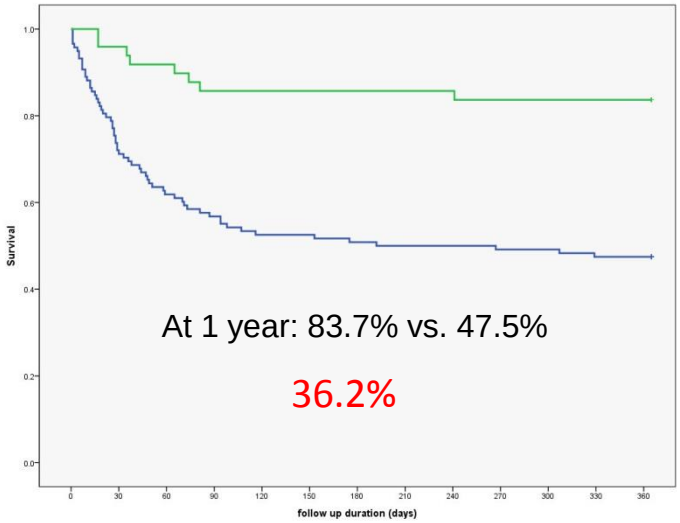
Transplant-free survival

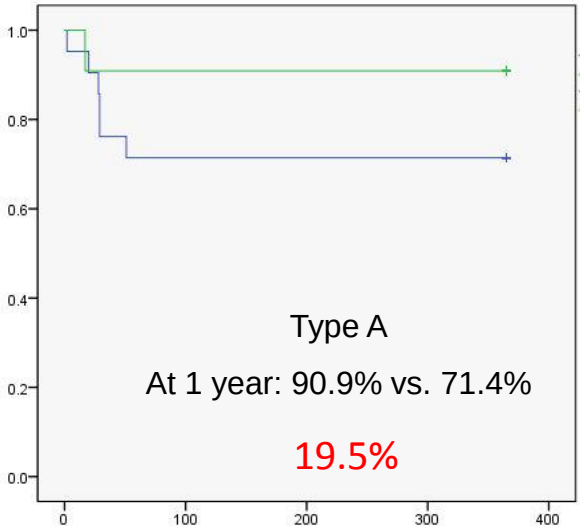


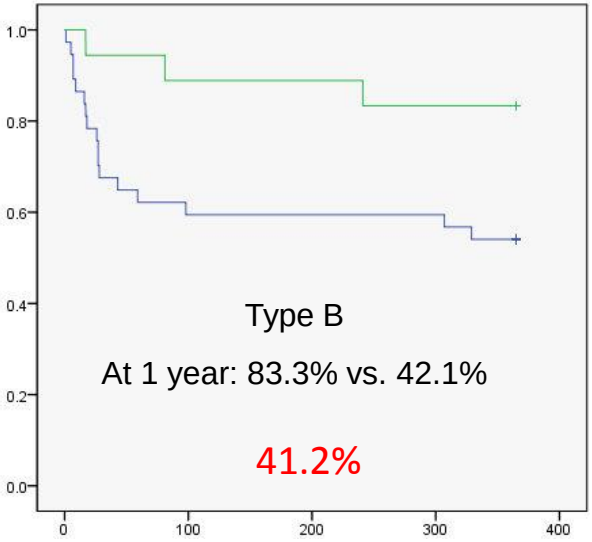
No additional mortality after initial early period for type A
Additional mortality even after 90 days for type B/C

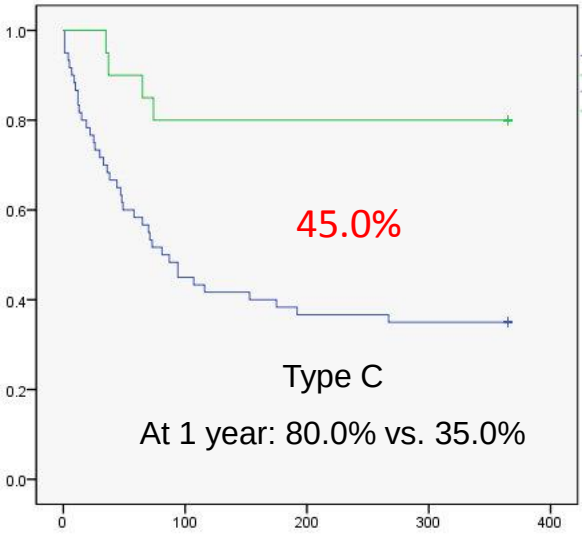
Hong YS et al., Intrim review

Survival by ACLF type and transplantation









Hong YS et al., Intrim review

Characteristics by ACLF types

	Type A N=32	Type B N=55	Type C N=80	P-value
Age (year)	51.8±10.4	53.9 ±10.2	58.0 ±11.1	0.010
Male	20 (62.5)	32 (58.2)	59 (73.8)	0.15
PREDISPOSITION				<0.001
HBV	**20 (62.5)**	20 (36.4)	28 (35.0)	
Alcohol	4 (12.5)	**25 (45.5)**	**33 (41.3)**	
HCV	0 (0)	0 (0)	6 (7.5)	
Autoimmune	**6 (18.8)**	2 (3.6)	2 (2.5)	
Others	2 (6.3)	8 (14.5)	11 (13.8)	

Hong YS et al., Intrim review

Characteristics by ACLF types

	Type A	Type B	Type C	P-value
HBV flare	**16 (50.0)**	**12 (21.8)**	4 (5.0)	< 0.001
Alcohol	3 (9.4)	**19 (34.5)**	6 (7.5)	< 0.001
HAV	3 (9.4)	1 (1.8)	1 (1.3)	0.061
Toxin	**5 (15.6)**	9 (16.4)	3 (3.8)	0.031
AIH flare	**7 (21.9)**	2 (3.6)	0 (0.0)	< 0.001
Infection	0 (0.0)	**13 (23.6)**	**32 (40.0)**	< 0.001
Varix bleeding	0 (0.0)	3 (5.5)	**11 (13.8)**	0.038
Other bleeding	0 (0.0)	2 (3.6)	6 (7.5)	0.21
Unknown	3 (9.4)	5 (9.1)	**23 (28.8)**	0.005

Hong YS et al., Intrim review

Characteristics by ACLF types

	Type A N=32	Type B N=55	Type C N=80	P-value
RESPONSE				
MELD score	29.2 ± 8.4	27.1 ± 5.7	26.3 ± 6.3	0.11
SIRS	9 (28.1)	19 (34.5)	30 (37.5)	0.64
Organ failures by CLIF-SOFA				
Specific organ type				
Hepatic	**25 (78.1)**	**43 (78.2)**	28 (35.0)	< 0.001
Coagulation	9 (28.1)	12 (21.8)	21 (26.3)	0.76
Cerebral	2 (6.3)	4 (7.3)	11 (13.8)	0.33
Renal	7 (21.9)	5 (9.1)	17 (21.3)	0.14
Circulatory	1 (3.1)	4 (7.3)	**16 (20.0)**	0.018
Respiratory	2 (6.3)	1 (1.8)	4 (5.0)	0.53
Type of organ failure				<0.001
None	7 (21.9)	9 (16.4)	28 (35.0)	
Hepatic	**13 (40.6)**	**26 (47.3)**	**11 (13.8)**	
Hepatic + extrahepatic	12 (37.5)	17 (30.9)	17 (21.3)	
Extrahepatic	**0 (0)**	**3 (5.5)**	**24 (30.0)**	

Hong YS et al., Intrim review

ACLF type

Reversibility is a concern

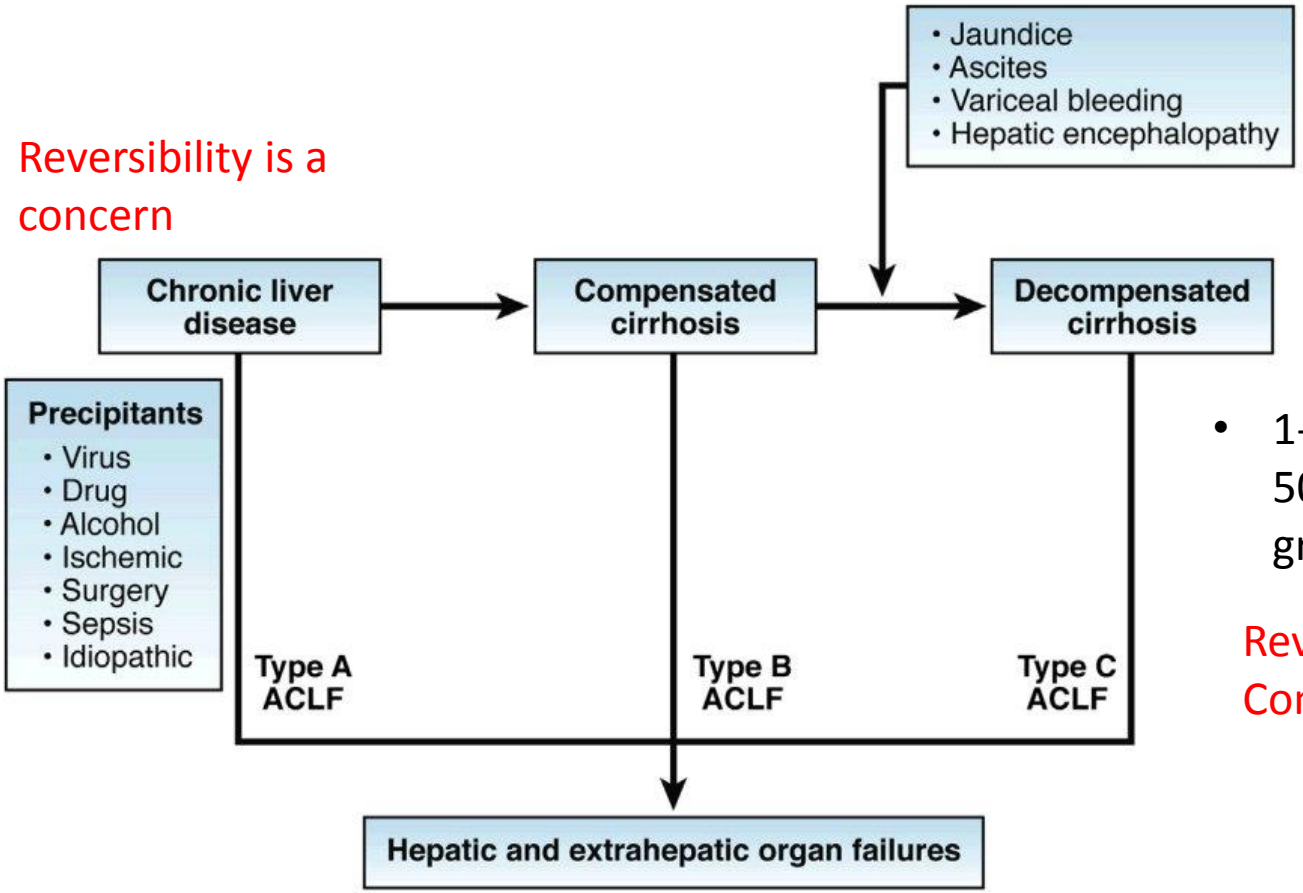


Figure 1. Proposed unifying pathogenesis for different types of acute-on-chronic liver failure (ACLF).

- 1-year of 15% & 5-year 50% mortality for grade 2-3 ascites

Reversibility?
Contraindicated for LT?

Jalan R et al., Gastroenterology 2014;147:4

Differences

	ALF	ACLF
Underlying liver disease	No	Yes
Definition of liver failure	Coagulopathy	Coagulopathy + Jaundice
Extrahepatic organ failure	Encephalopathy	Encephalopathy Kidney Lung Circulation
Subtype	No	A, B, C

Summary

- Acute liver failure
  - **Coagulopathy**
  - **Encephalopathy**

- Acute on chronic liver failure
  - Chronic liver disease (type A,B,C)
  - Acute deteriorated liver function (jaundice + coagulopathy)
  - Extrahepatic organ failure (encephalopathy and others…)

Take home message #1

- Definition and classification of liver failure
  - Acute liver failure
  - Acute on chronic liver failure
    - Type A
    - Type B
    - Type C

Today's content

- Definition and classification of liver failure
- Things to consider in acute liver failure
- Things to consider in acute on chronic liver failure

Things to consider in acute liver failure

- The dangerous signal: **Encephalopathy**
- Specific management? → look for etiology
- High volume plasmapheresis?

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases

American Association for the Study of Liver Diseases *,†
European Association for the Study of the Liver*,†

Definition of HE

Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or PSS; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma

Type	Grade		Time course	Spontaneous or precipitated
A	MHE	Covert	Episodic	Spontaneous
	1			
B	2	Overt	Recurrent	
	3			Precipitated (specify)
C	4		Persistent	

HE type A (HE in ALF)

Cerebral Edema/Intracranial Hypertension

Grade I/II Encephalopathy

- Consider transfer to liver transplant facility and listing for transplantation
- Brain CT: rule out other causes of decreased mental status; little utility to identify cerebral edema
- Avoid stimulation; avoid sedation if possible
- Antibiotics: surveillance and treatment of infection required; prophylaxis possibly helpful
- Lactulose, possibly helpful

Grade III/IV Encephalopathy

- Continue management strategies listed above
- Intubate trachea (may require sedation)
- Elevate head of bed
- Consider placement of ICP monitoring device
- Immediate treatment of seizures required; prophylaxis of unclear value
- Mannitol: use for severe elevation of ICP or first clinical signs of herniation
- Hypertonic saline to raise serum sodium to 145-155 mmol/L
- Hyperventilation: effects short-lived; may use for impending herniation

2011 AASLD Guideline Acute liver failure

Why look for etiology?

- N-actylcystein for acetaminophen, drug, HBV
- Steroid for autoimmune hepatitis, drug
- Antiviral agents for viral hepatitis

Acute liver failure (ALF)

- Drug induced-ALF (DI-ALF)
  - Intrinsic hepatotoxin (acetaminophen...)
  - Idiosyncratic drug reactions (presumably immune-mediated liver injury due to the metabolic generation of a neo-antigen)

Smith et al., Lancet 1993;342:963: Stravitz et al., Hepatology 2011;53:517

Steroid Use in Acute Liver Failure

Jamuna Karkhanis,[1] Elizabeth C. Verna,[1] Matthew S. Chang,[1] R. Todd Stravitz,[2] Michael Schilsky,[3] William M. Lee,[4] and Robert S. Brown, Jr.,[1] for the Acute Liver Failure Study Group

- Retrospective analysis
- Patients
  - AI-ALF (n = 66)
  - DI-ALF (n = 131, non-acetaminophen)
  - Indeterminate (n = 164)
- Steroid use
  - AI-ALF (25/66, 38%)
  - DI-ALF (16/131, 12%)
  - Indeterminate (21/164, 13%)

Karkhanis et al., Hepatology 2014;59:612

Steroid use in potentially immune mediated ALF

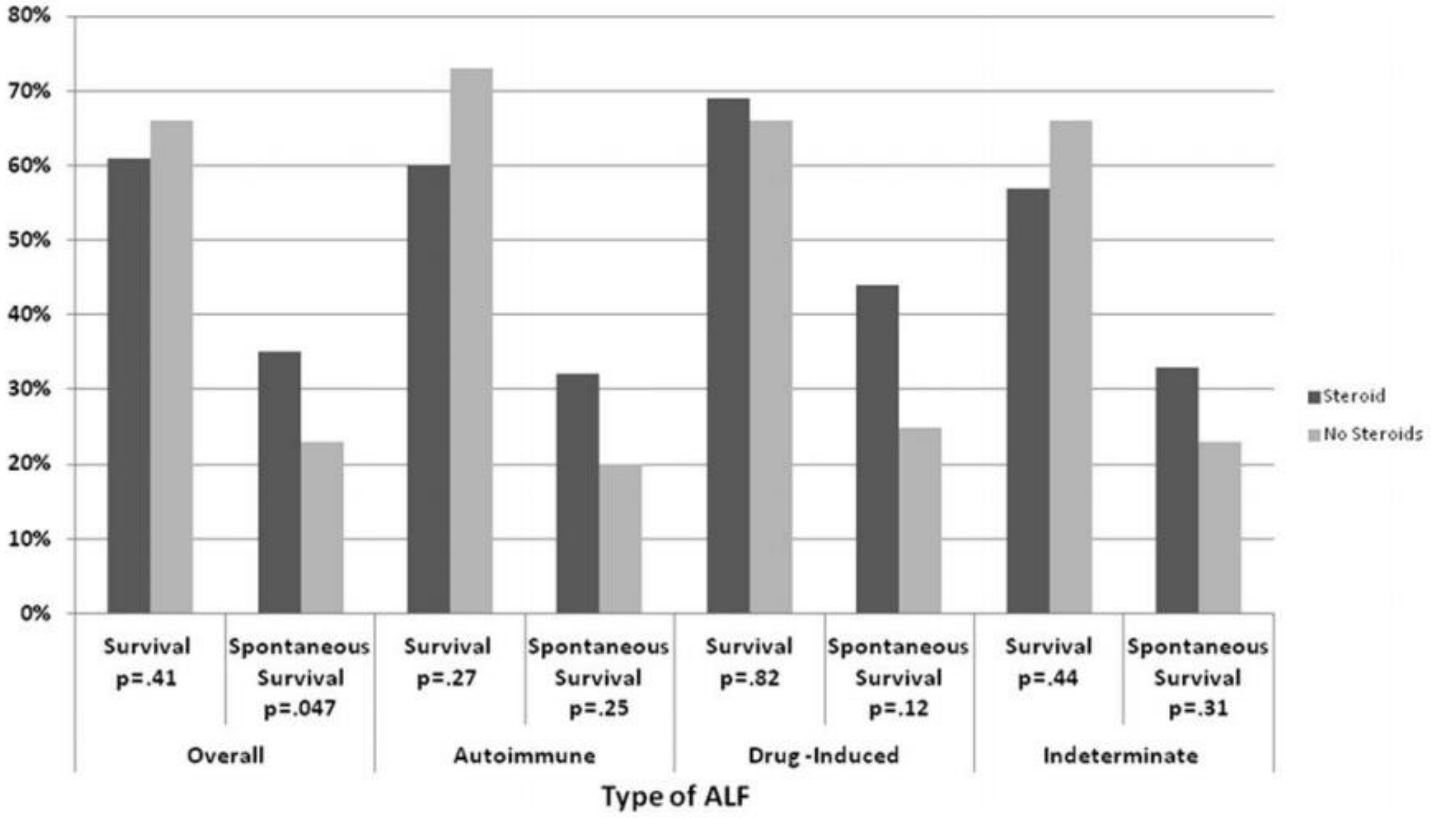
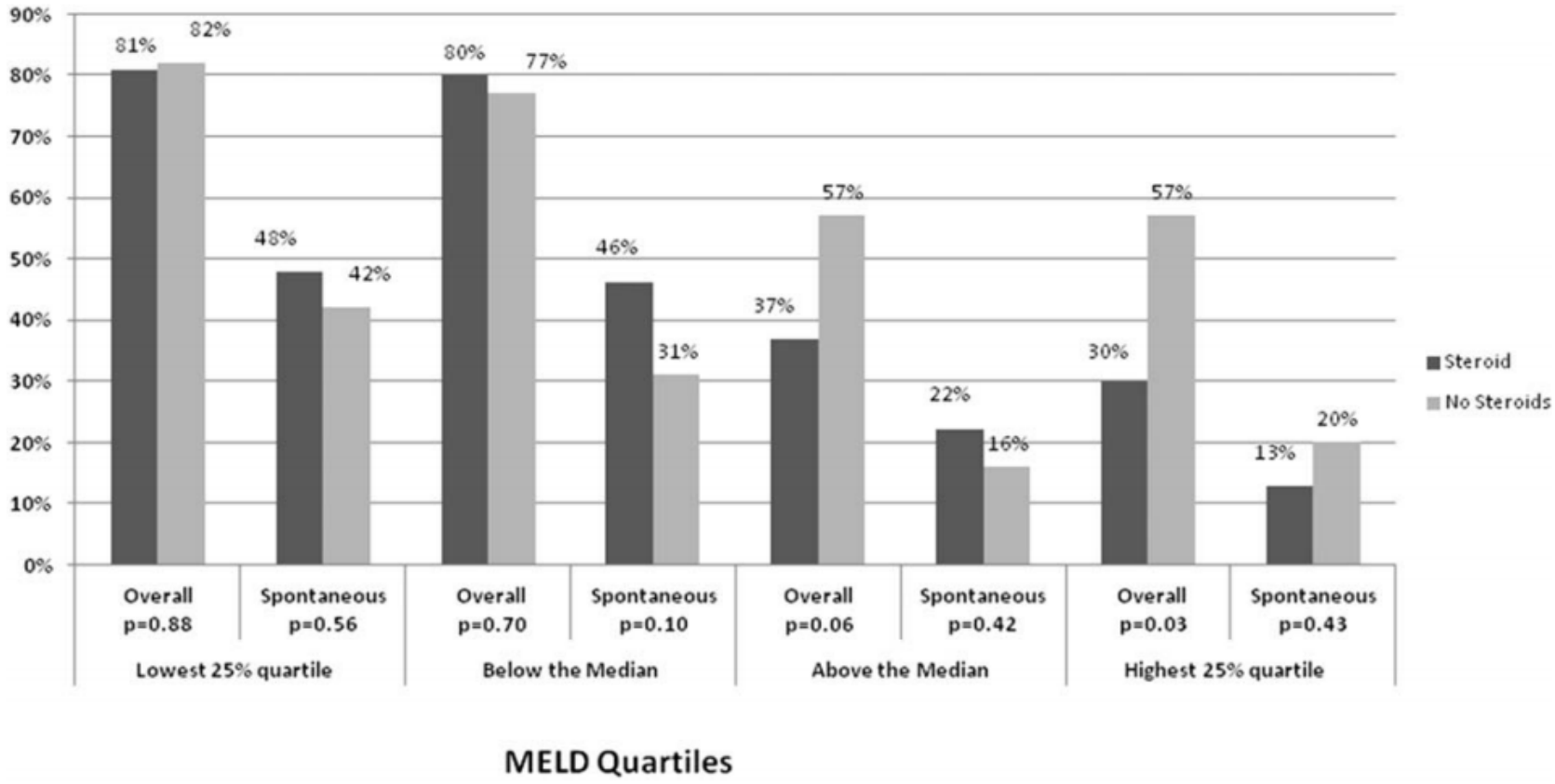


Fig. 1. Overall and spontaneous survival among different etiologies of ALF.

Karkhanis et al., Hepatology 2014;59:612

Steroid use in potentially immune mediated ALF



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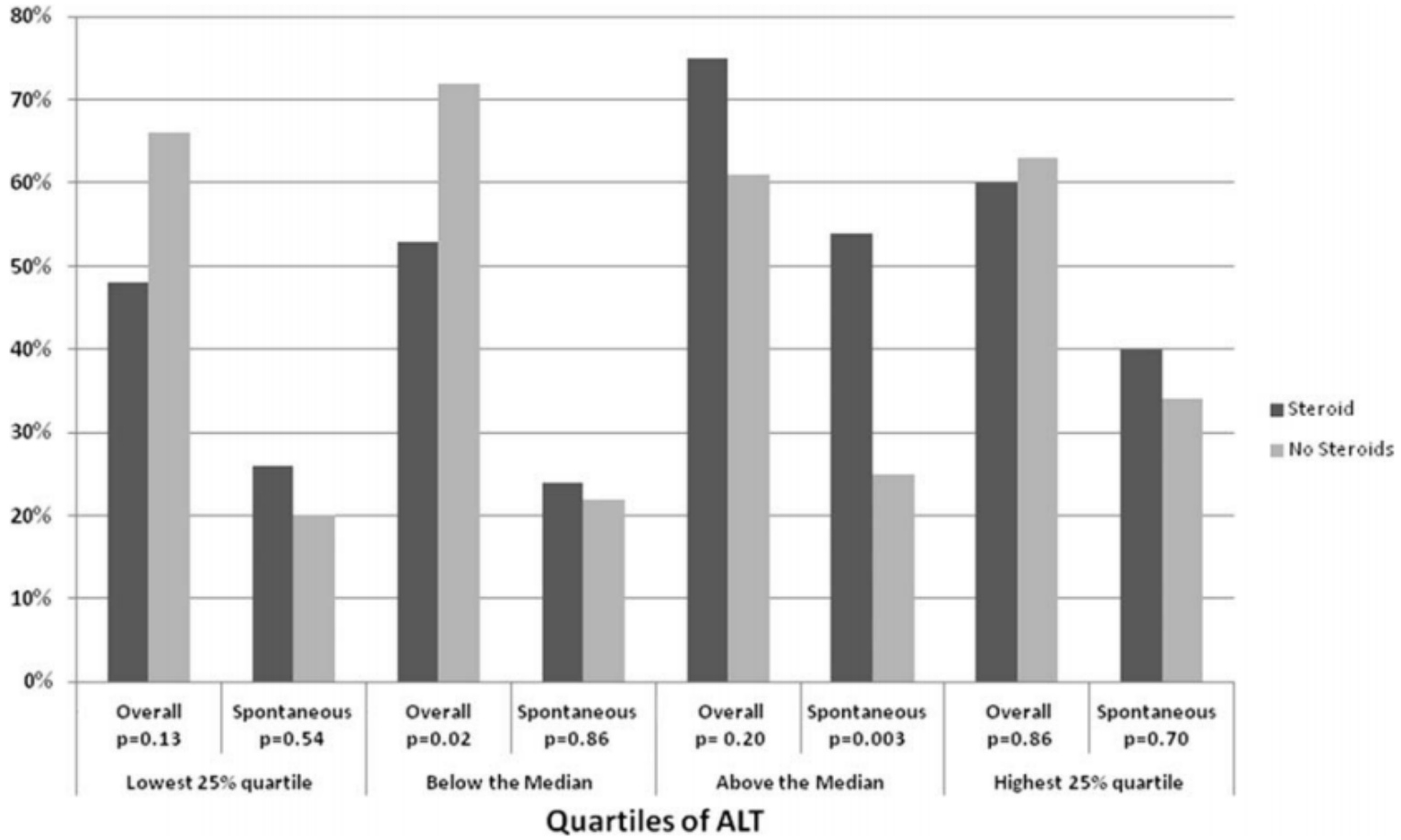


Karkhanis et al., Hepatology 2014;59:612

Steroid use in DI-ALF

- Data suggest.
  - High MELD patients, may not benefit from steroid
  - High AST/ALT, may help identify patients who will likely to respond from steroid
- Controversial.

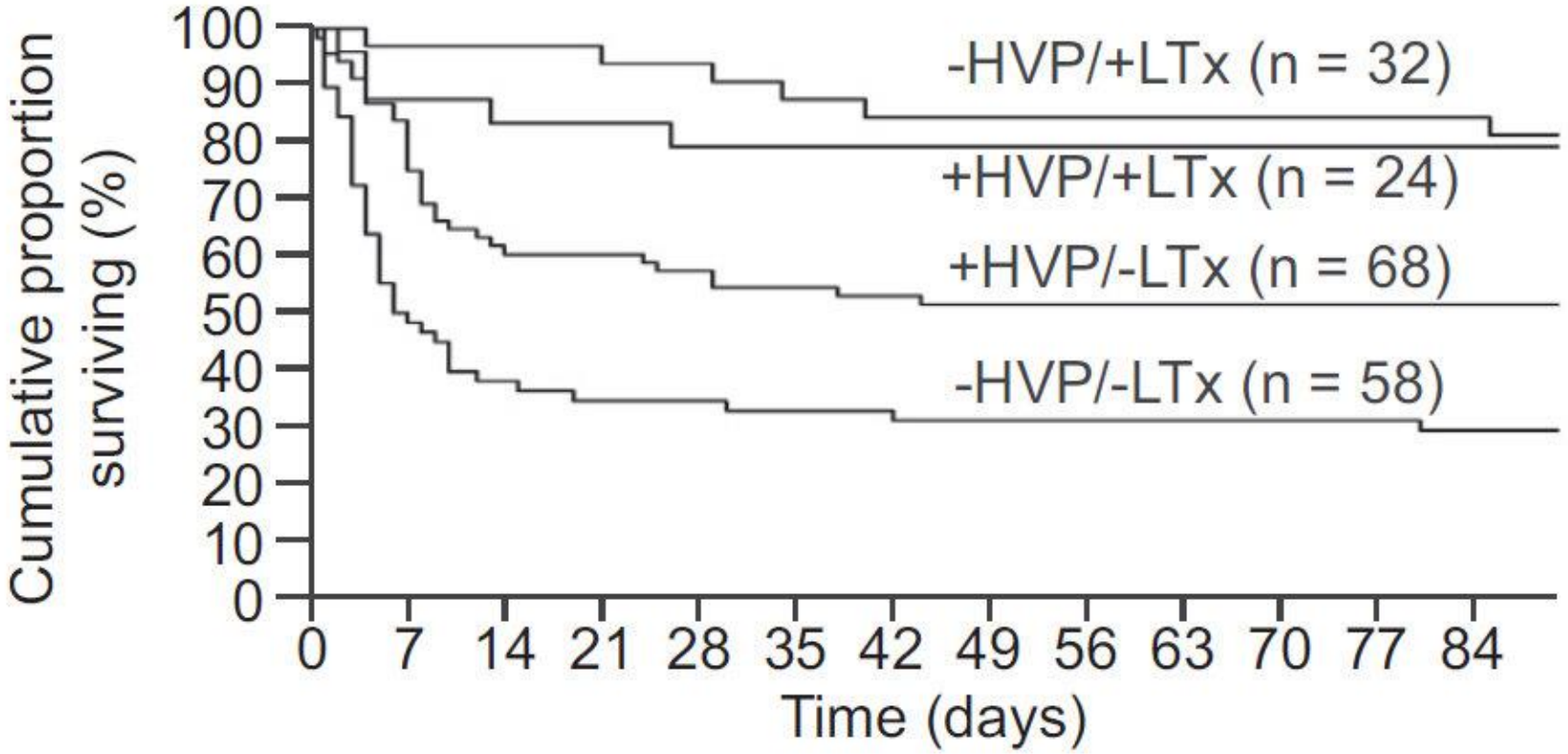
High volume plasmapheresis (HVP)

- HVP can remove albumin bound toxins as well as unbound toxins, including aromatic amino acids, ammonia, endotoxin, indols, mercaptans, phenols, and other factors which may be responsible for hepatic coma, hyperkinetic syndrome, and decreased systemic vascular resistance and cerebral blood flow.

- Improved cerebral blood flow, mean arterial, pressure (MAP), cerebral perfusion pressure, cerebral metabolic rate, increased hepatic blood flow, and improvements in other laboratory parameters such as cholinesterase activity or galactose elimination capacity.

Schwartz et al., J Clin Apher 2016;31:149

RCT that took more than 12 years



Larsen et al., J Hepatol 2016

Journal of Clinical Apheresis 31:149–338 (2016)

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue

ACUTE LIVER FAILURE

Incidence: < 10/1,000,000/yr		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2B	III
		TPE-HV	Grade 1A	I
No. of reported patients: > 300	**RCT**	**CT**	**CS**	**CR**
TPE	1(120)	1(158)	40(878)	54(73)
TPE-HV	1(182)	NA	NA	NA

TPE-HV: TPE-High Volume, not available in US.

Today's content

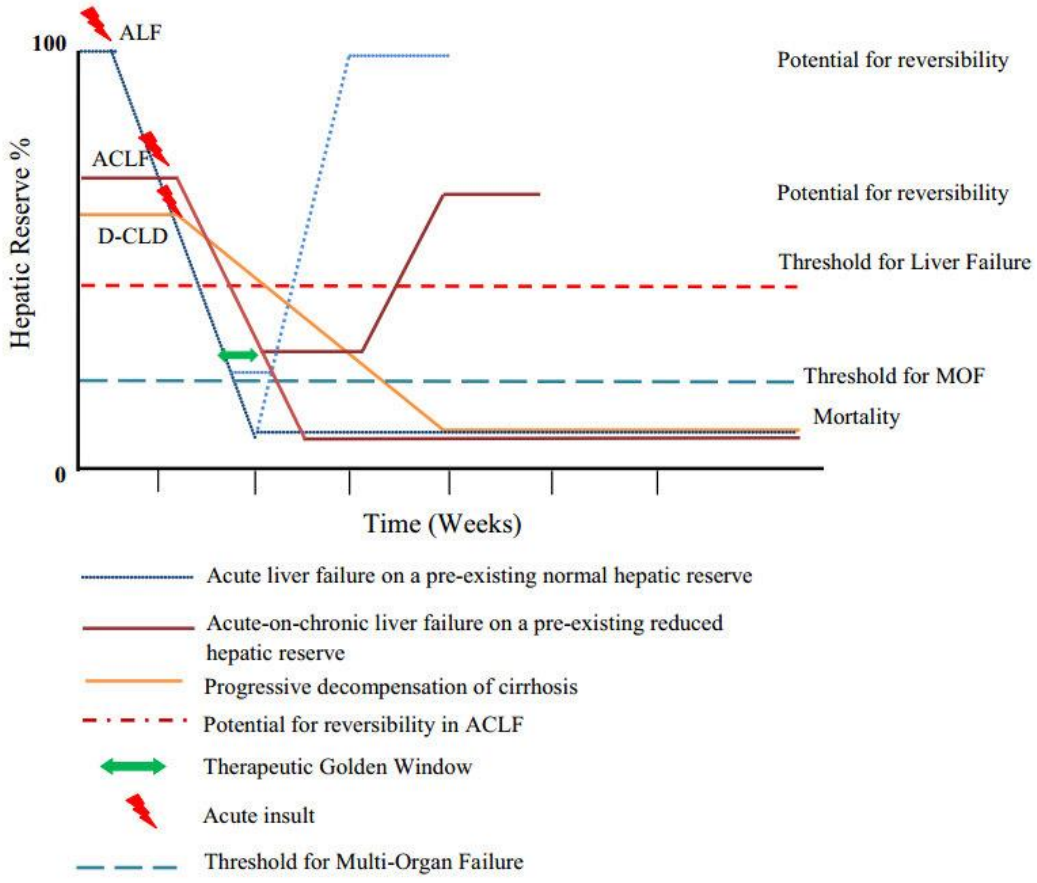
- Definition and classification of liver failure
- Things to consider in acute liver failure
- Things to consider in acute on chronic liver failure

Things to consider in acute on chronic liver failure

- Specific management? → look for trigger

- Critically ill patients with cirrhosis need a multidisciplinary approach

ACLF management



Trigger-specific management

Sarin et al., Hepatol Int 2014;8:453

Events known to precipitate ACLF

- Acute hepatotrophic viral infection
  - Acute hepatitis A, B, D, E
  - Reactivation of hepatitis B
- Alcoholic hepatitis
- Drug induced liver injury
- Infection
- Gastointestinal bleeding
- Ischemia

Asrani et al., Clin Liver Dis 2014;18:561

Seminar

JOURNAL OF HEPATOLOGY

Management of the critically ill patient with cirrhosis: A multidisciplinary perspective

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J Hepatology 2016;64:717

Key recommendations for AKI

- Replacement of
  - isotonic crystalloids in cases of volume loss due to diarrhea or over diuresis (1D)
  - blood in cases of acute gastrointestinal hemorrhage (1D),
  - 20–25% albumin for infections (1A), suspected type-1 HRS (1A) or in cases where the cause of AKI is unclear (1D).
- RRT indication
  - worsening AKI, worsening fluid overload with >10% total body weight despite diuretic therapy or worsening acid-base status (1D).

Nadim et al., J Hepatology 2016;64:717

Key recommendations for Cardio-pulmonary dysfunctions

- a mean arterial pressure 60 mmHg is usually appropriate (1D).
- therapeutic paracentesis in patients with tense ascites (1A).
- careful attention and monitoring of patients, preferably with a pulmonary artery catheter (PAC) or echocardiography, during fluid resuscitation to avoid development of fluid overload (1D).
- repeated measurements of blood lactate levels even though the interpretation may be complicated by the impaired clearance in cirrhosis (1A).

Nadim et al., J Hepatology 2016;64:717

Key recommendations for choice of fluid

- crystalloid solutions as the initial fluid of choice in volume depleted patients (10–20 ml/kg) (1C).
- albumin (8 g/L of ascites removed) following large volume paracentesis (>5 L) (1B).
- concentrated albumin (1.5 g/kg on day one followed by 1 g/kg on day 3) for SBP (1B). → *보험급여됨 (단 cr > 1mg/dL, BUN > 30mg/dL, Bilirubin > 4 mg/dL 이어야 함)*
- crystalloids and a proportion of 4–5% albumin may be an option for suspected bacterial infection (2D).
- recommend against the use of hydroxyethyl starch (HES) (1B).

Nadim et al., J Hepatology 2016;64:717

Key recommendations for shock

- norepinephrine as the first line vasopressor agent (1A).
- Vasopressin or terlipressin are appropriate second line agents for persistent hypotension (1B).
- A trial of hydrocortisone 200–300 mg/day in divided doses in patients with refractory hypotension should be started and stopped following improvement in hemodynamics (1C).

Nadim et al., J Hepatology 2016;64:717

Key recommendations for antibiotics prophylaxis

- universal decontamination with intranasal mupirocin (twice daily) and chlorhexidine baths of ICU patients as part of a hospital wide plan to decrease bloodstream infections (2B).

Nadim et al., J Hepatology 2016;64:717

Key recommendations for risk of bleeding

- INR does not provide an adequate assessment of hemostasis in cirrhosis (2B).
- recommend against routine prophylactic use of fresh frozen plasma (FFP) (1B).
- maintaining platelet counts above 50 X 10^9/L in the presence of active bleeding (2C).
- hemoglobin transfusion trigger of 7 mg/dl (1A).
- anticoagulation with unfractionated/low molecular weight heparin in patients with occlusive portal vein thrombosis in the absence of bleeding risk factors (2C).
- maintaining fibrinogen levels >1.5 g/L in patients with significant bleeding or during invasive/surgical procedures (2C).

Nadim et al., J Hepatology 2016;64:717

Take home message #2

- ALF management
  - **Encephalopathy**
  - Look for etiology
  - Consider high volume plasmapheresis
- ACLF management
  - Look for trigger
  - Multidisciplinary approach for organ failures