Management of HBV Flares and Acute on Chronic Liver Failure (ACLF)

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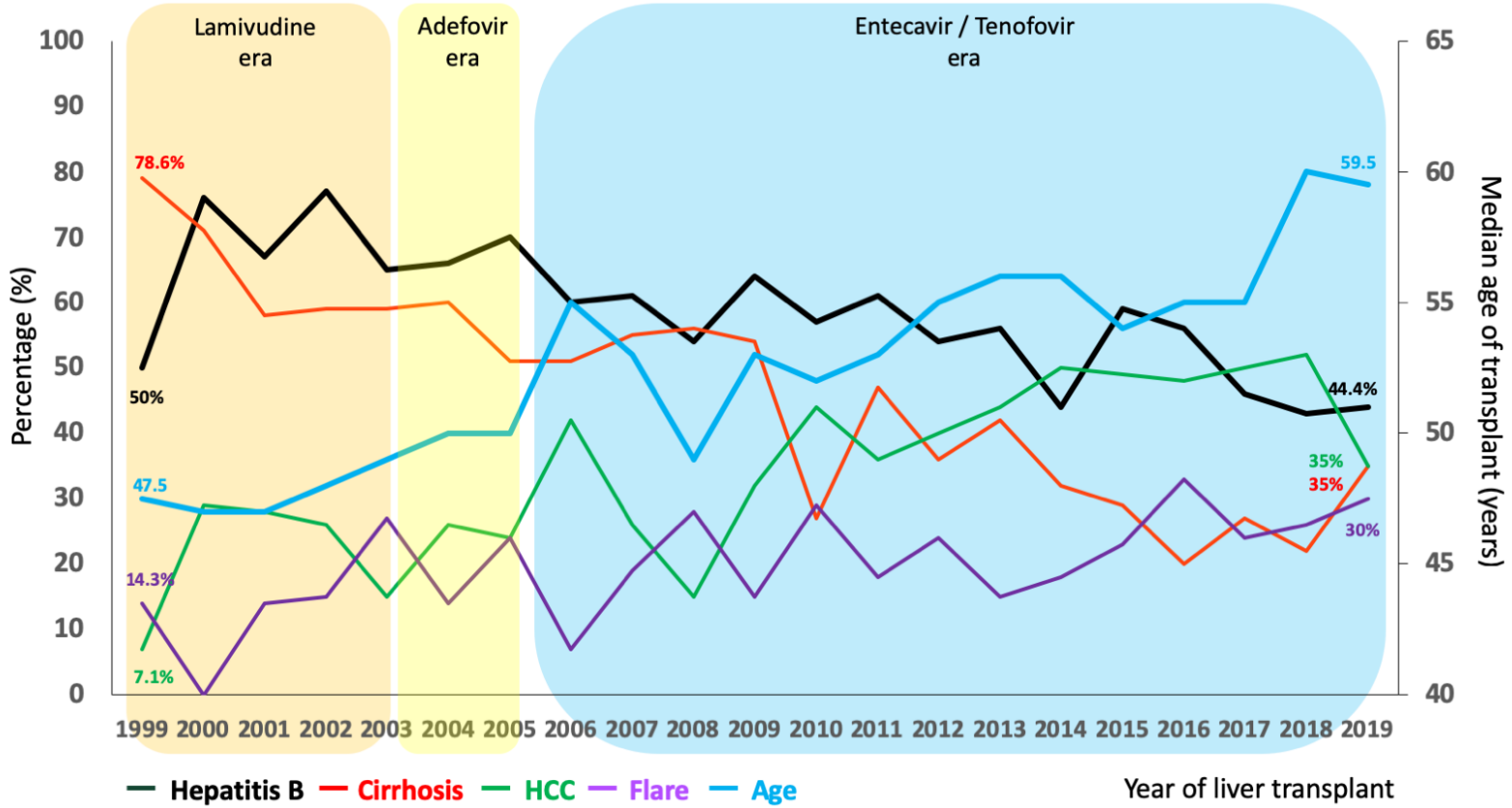
Impact of Oral Antiviral Use in Liver Transplantation for CHB in Hong Kong

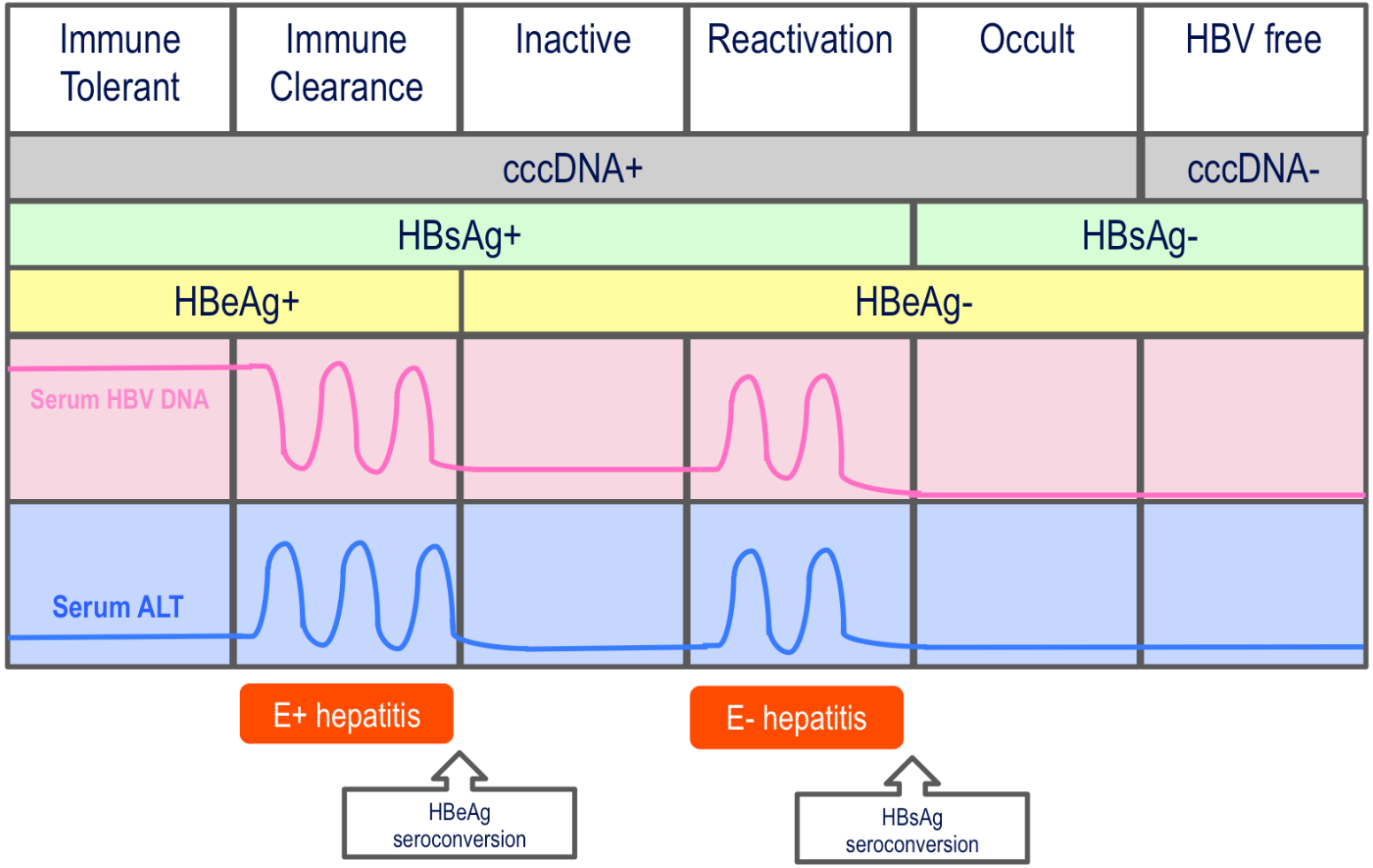
Despite NUCs being available for over two decades, severe acute flares continues to be a major health burden, and a significant indication for liver transplantation in CHB patients.



- Spontaneous
- During antiviral therapy
  - Drug-resistance
  - Non-compliance
- After antiviral therapy
  - Stopping therapy
- Immunosuppression
- Others
  - HIV (treated with ART)
  - HCV (treated with DAA)
  - Anti-TB
  - Pregnancy
  - IFN

J Fung et al. Liver Transpl 2020 (in press)

Natural History of CHB Infection and Flares



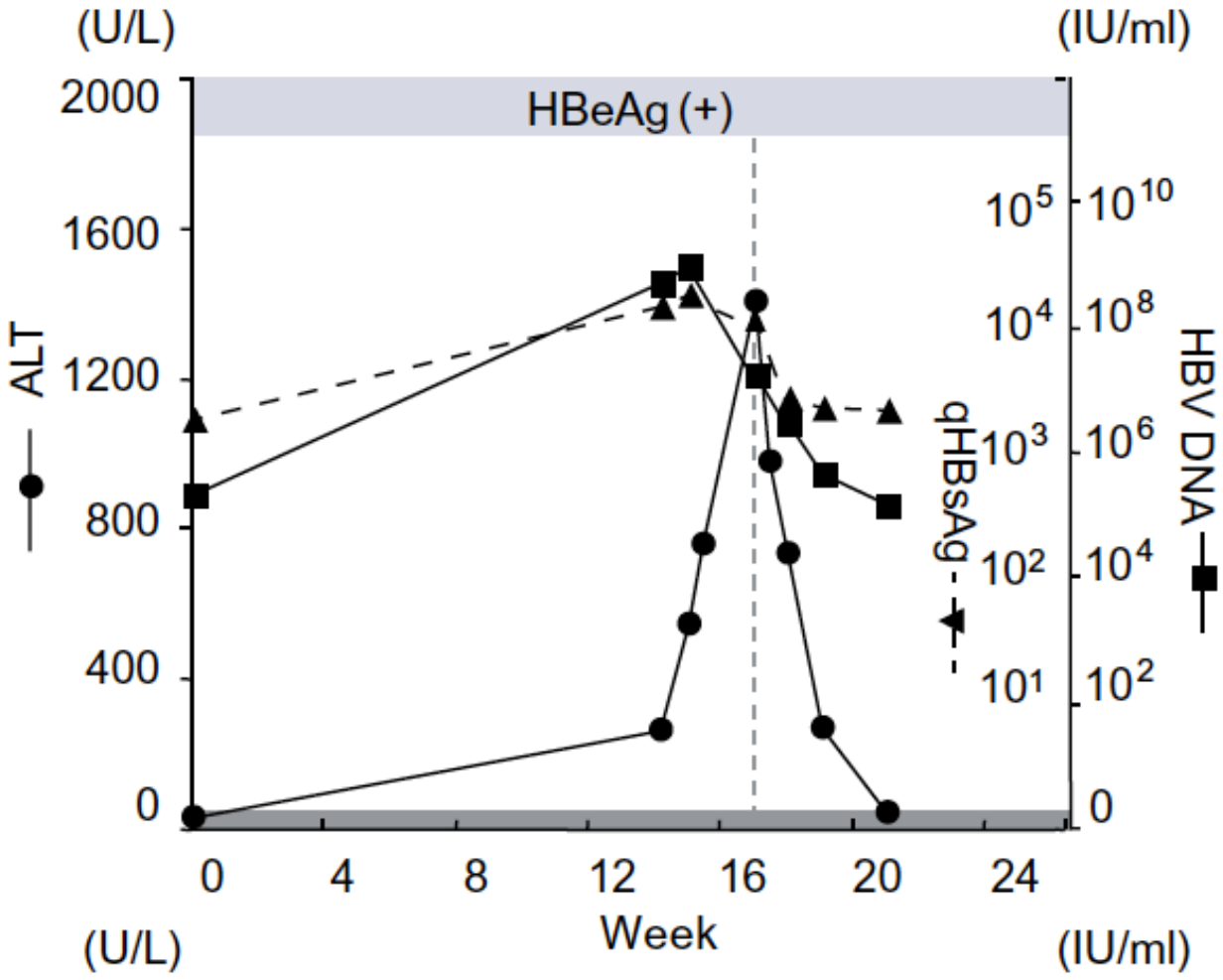
- Around age 20-40, majority of CHB patients will undergo immune clearance of HBV
- Annual incidence of flares
  - E+ 27%
  - E- 10%

J Fung et al. Expert Opin Emerg Drugs 2014

Acute Flares of Chronic Hepatitis B

- No consensus definition of flare/exacerbation of CHB
  - Characterized by sudden elevation of ALT
  - >3x increase from baseline or >5x ULN ALT
- Liver biopsies during flares shows lobular necro-inflammatory changes, distributed unevenly
  - Bridging hepatic necrosis (BHN) may occur in more severe cases
  - Submassive/massive necrosis is usually found in liver explants
- Acute flare likely due to changes in the immunological control of HBV replication

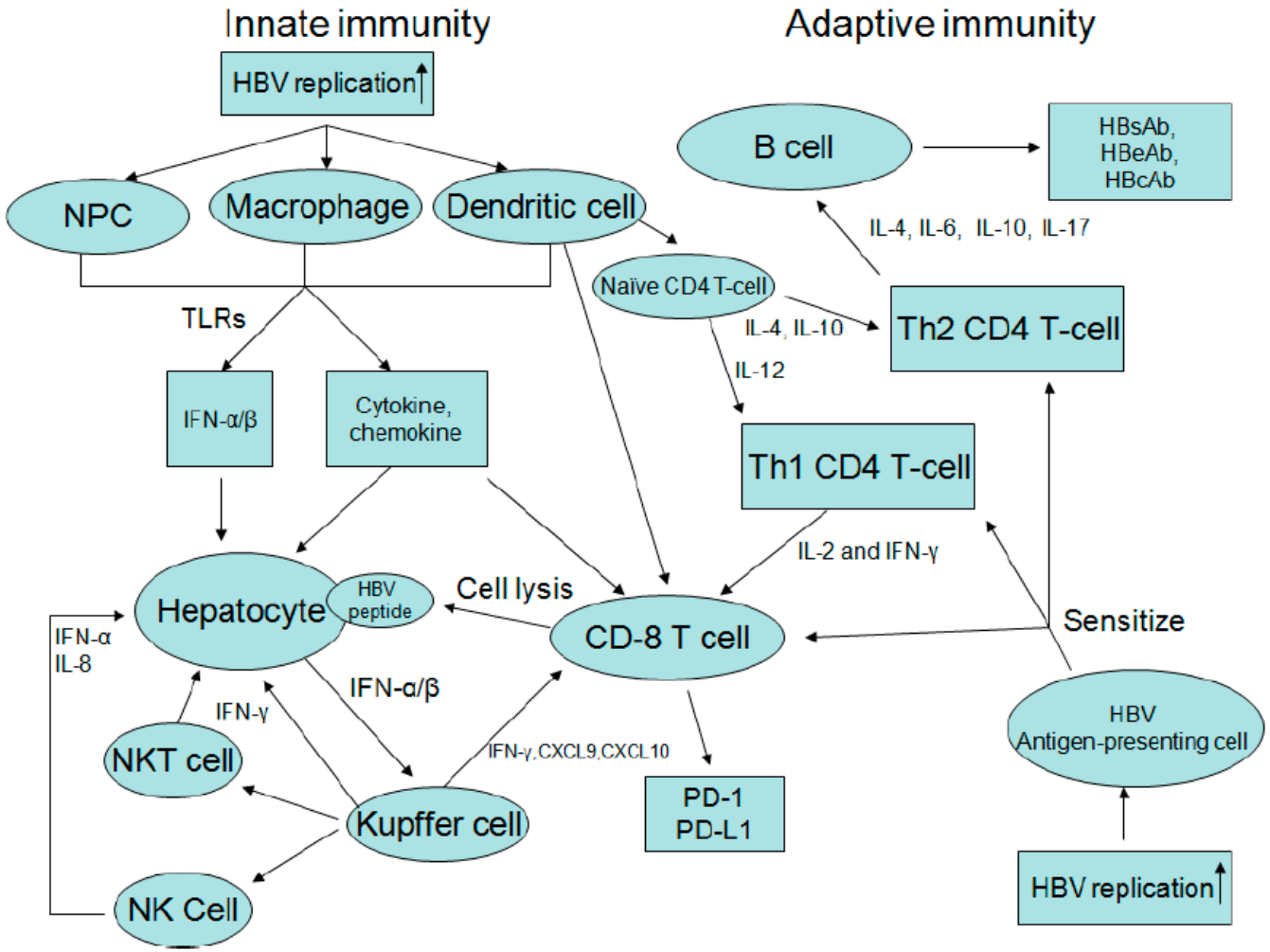
Serological & Immune Profile During HBV Flare



	↑ALT	Peak ALT	↓ALT
HBV DNA	↑/peak	↑/↓	↓/stable
HBeAg	↑/peak	↑/↓	↓/stable
HBeAg/HBcAg TCR	↑	↑	Peak/↓/stable
HBV-s Treg	↓	Nadir	↑
HBV-s Tc	↑	Peak	↓
IFN-γ. IL-2	↑	↑/peak	Peak/↓
IFN-α. IL-8	↑/peak	Peak/↓	↓
CXCL-9/10	↑	Peak	↓
IL-10	↑/peak	Peak/↓	↓
PD-1/PD-L1	↑	Peak	↓

ML Chang & YF Liaw. J Hepatol 2014

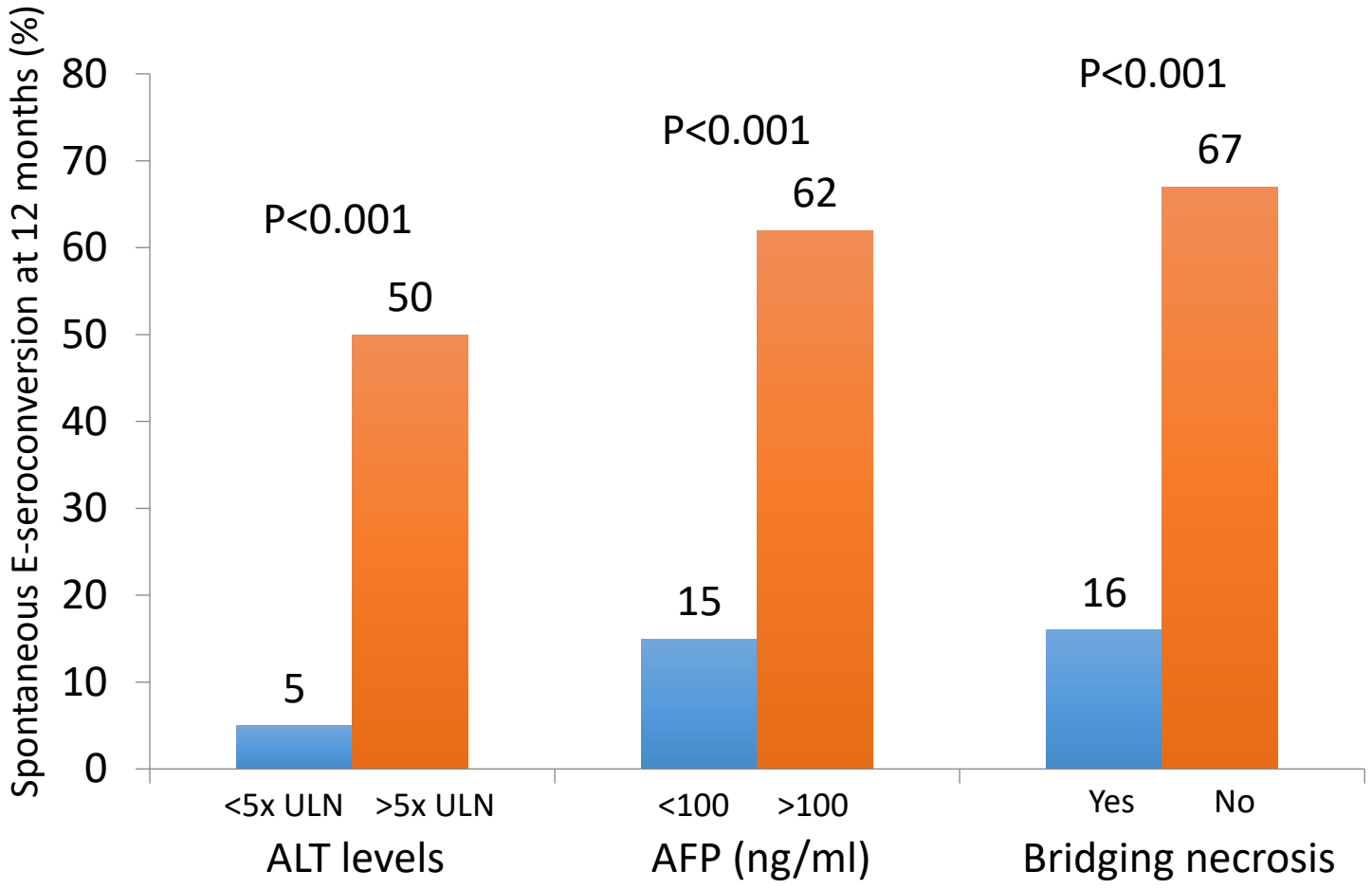
Dynamic Changes in Innate and Adaptive Immune Response During HBV Flare

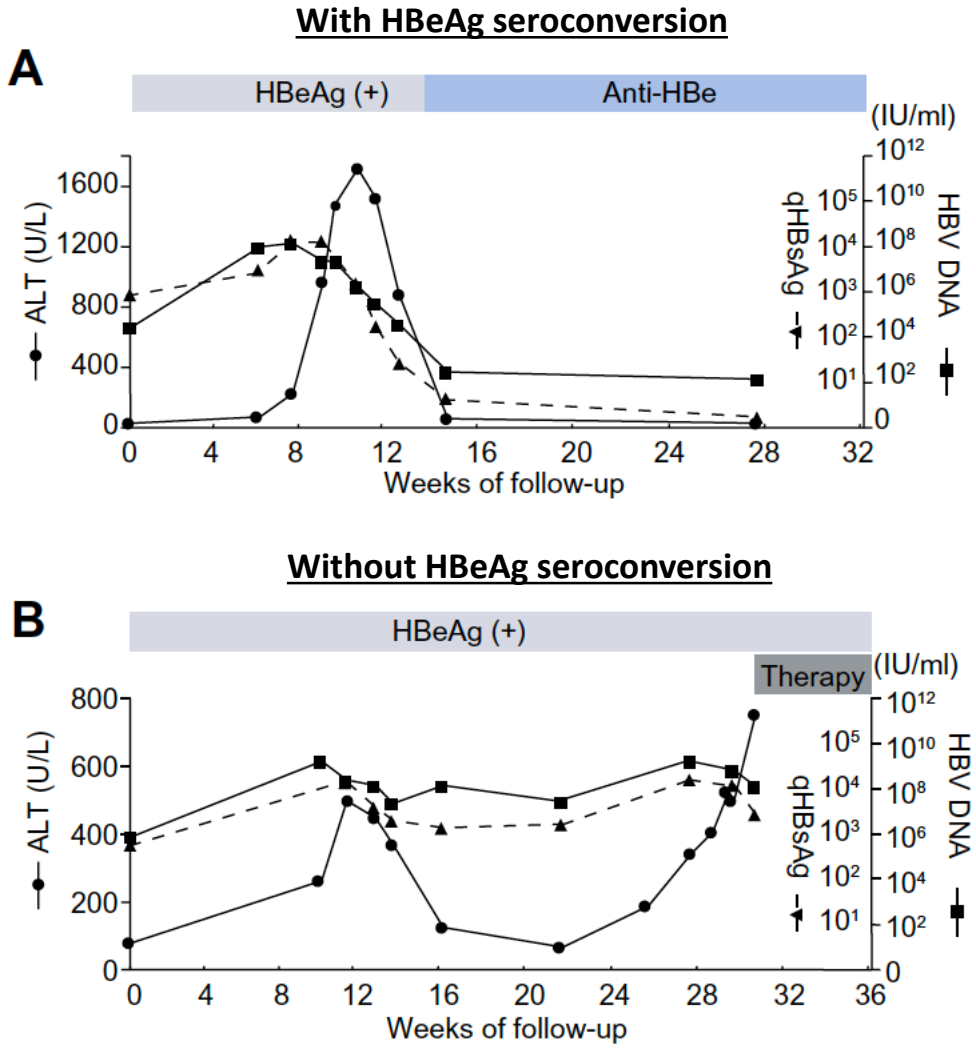


- Upsurge in HBV DNAs
- Liver injury mediated by T-cells sensitized by HBV antigen presenting cells
- Virus-specific CD8+ cytotoxic T cells (with help from CD4+ T cells) recognize viral antigens on infected hepatocytes – lead to cell lysis

WL Tsai et al. Int J Mol Sci 2015

Spontaneous HBeAg Seroconversion after Acute HBV Flares in HBeAg+ Patients





ML Chang & YF Liaw. J Hepatol 2014

Clinical Presentation of Acute Flares of CHB

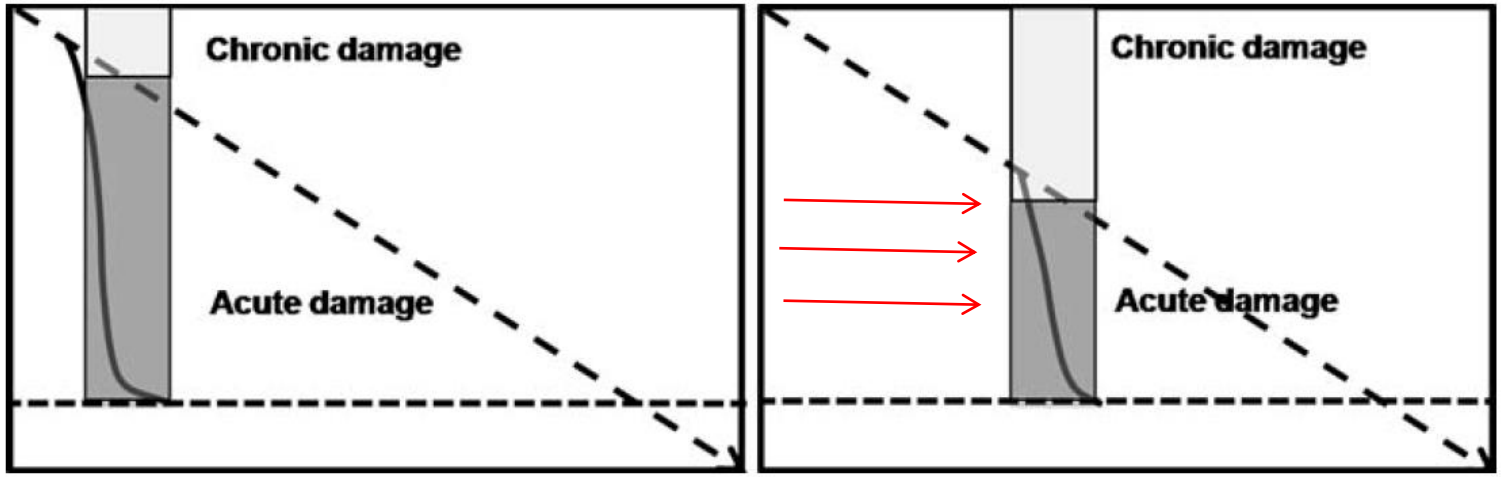
Asymptomatic
Normal bilirubin
Normal INR

Jaundice
Coagulopathy
Decompensation
ACLF
Death

Underlying established liver disease
(fibrosis/cirrhosis

Severity of flare
(Viral load/immune response)

Concurrent illnesses
(infections/sepsis)



Sarin SK et al, 2009. Hepatol Int

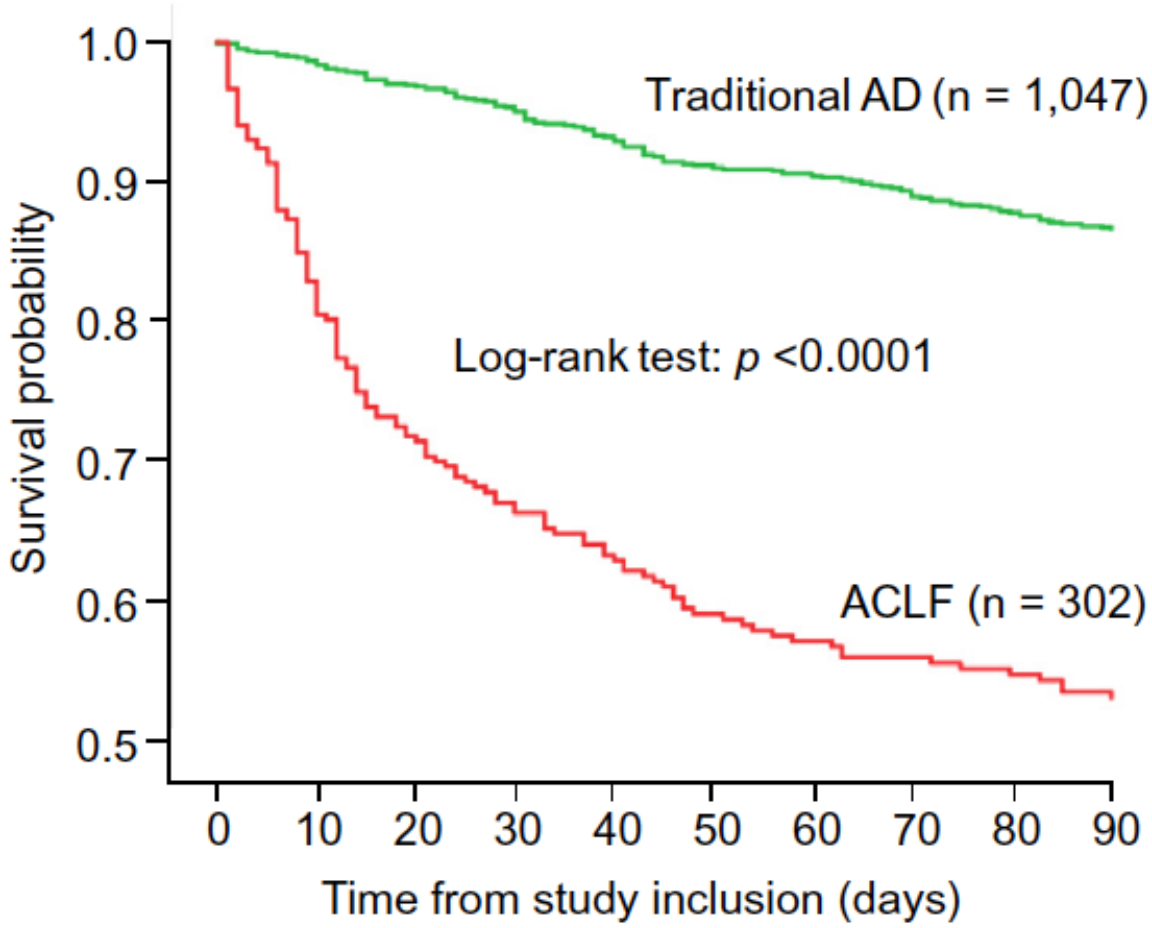
3 Major Definitions/Criteria from Different Cohorts

	APASL ACLF Research Consortium (AARC) 5228 patients 43 centers 15 countries Asia-Pacific Region	EASL-CLIF 1343 patients 29 centers 8 countries Europe	NACSELD 2675 patients 14 centers US & Canada North America
	Cirrhosis – not a requirement	Cirrhosis – Yes	
Organ Failure Definitions	Liver: Bilirubin >5mng/dL; Lactate Kidney: AKI Network criteria Brain: West-Haven HE grade 3-4 Coagulation: INR >1.5 Circulation: None Respiratory: None	Liver: Bilirubin >12 mng/dL Kidney: Cr >2.0 mg/dL or RRT Brain: West-Haven HE grade 3-4 Coagulation: INR >2.5 Circulation: Vasopressor Respiratory: PaO2/FiO2 <200 or MV	Liver: None Kidney: RRT Brain: West-Haven HE grade 3-4 Coagulation: None Circulation: MAP <60 mmHg Respiratory: MV
ACLF Definitions	Liver failure complicated within 4 weeks by ascites and/or HE	Grade 1: High-risk single organ failure Grade 2: Two organ failures Grade 3: Three organ failures	2 organ failures or more
Primary Driver of Liver Injury	Hepatic Eg: alcohol, viral hepatitis, DILI, AIH	Extra-hepatic Eg: infection/GI bleeding	

Definitions of Acute on Chronic Liver Failure

- "ACLF is an acute hepatic insult manifesting as jaundice (serum bilirubin ≥ 5 mg/dL (85 µmol/L) and coagulopathy (INR ≥ 1.5 or prothrombin activity < 40%) 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."

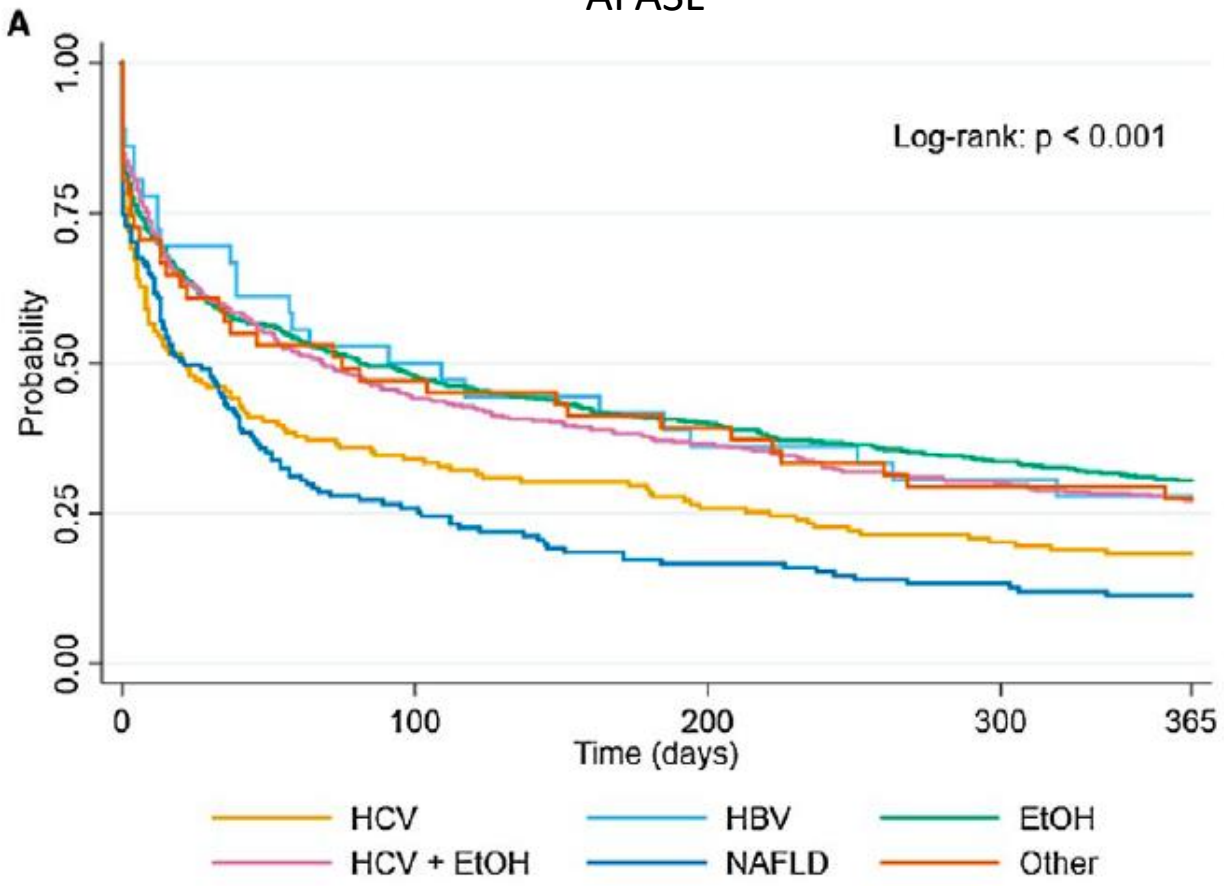
APASL 2019 Consensus Definition



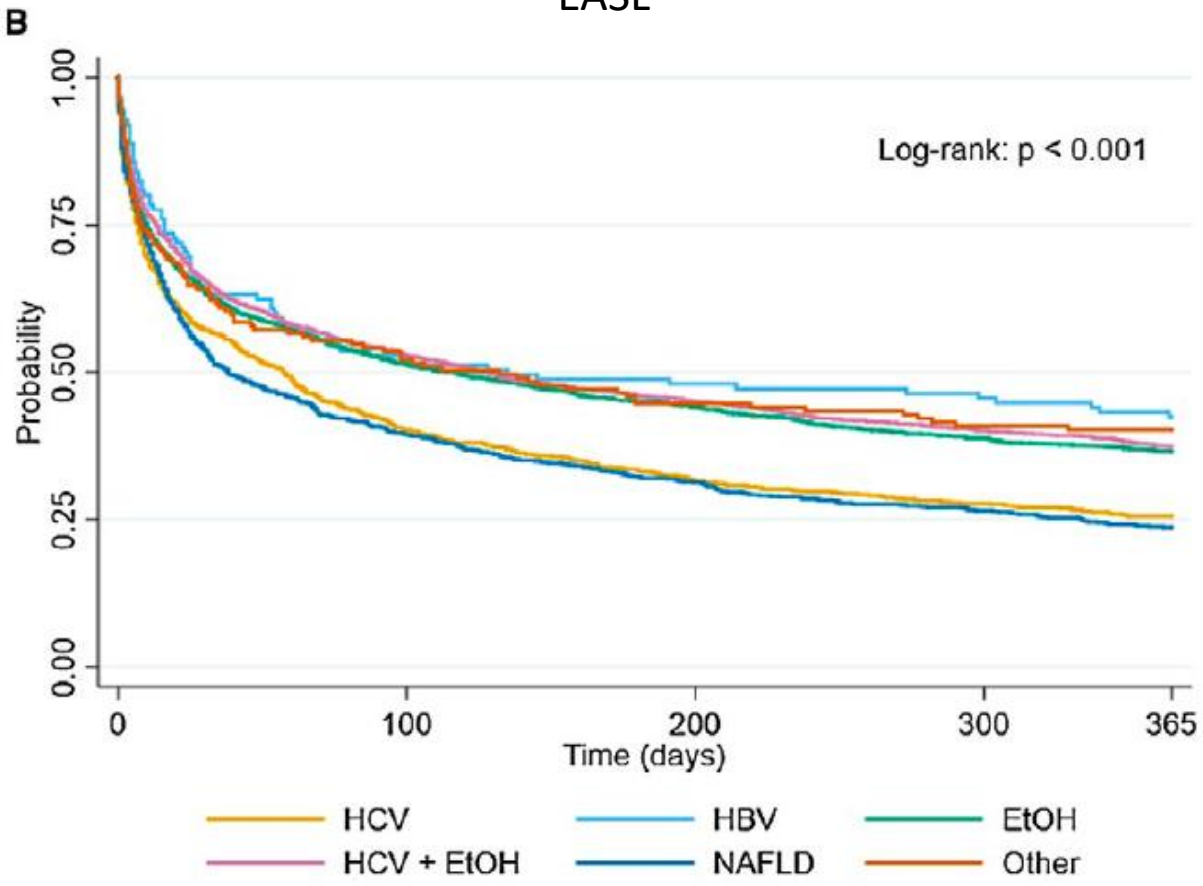
Gustot T & Moreau R. J Hepatology 2018

Survival in ACLF According to Underlying CLD

APASL

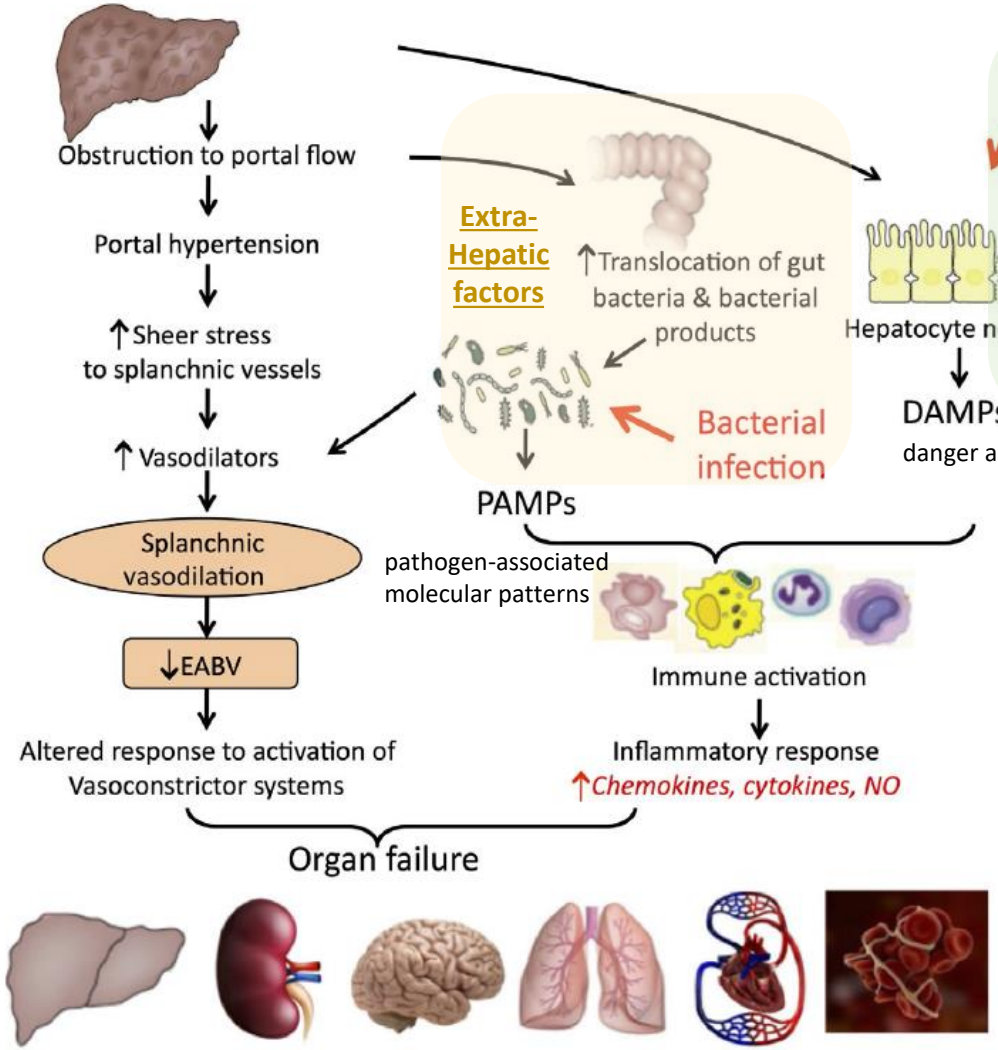


EASL

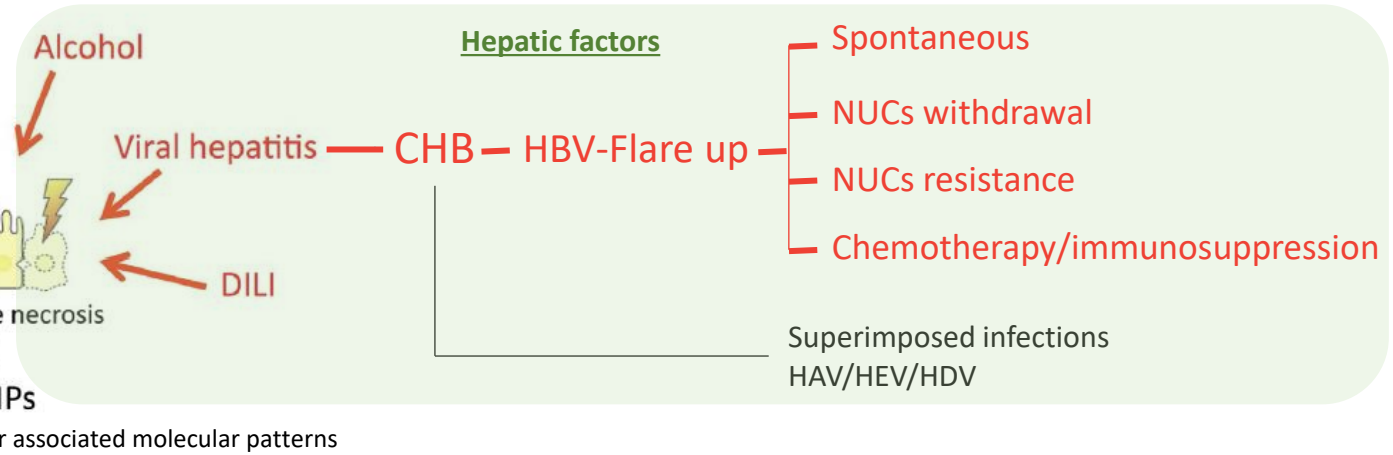


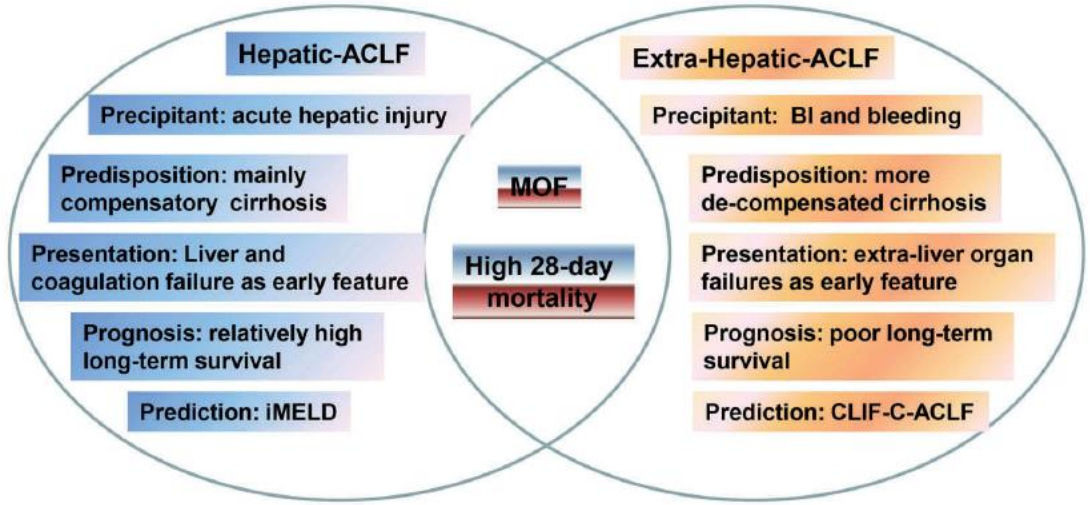
Mahmud N et al. Hepatology 2019

Pathophysiology of ACLF and Precipitating Events of HBV-related ACLF



Wong F. Clin Liver Disease 2019

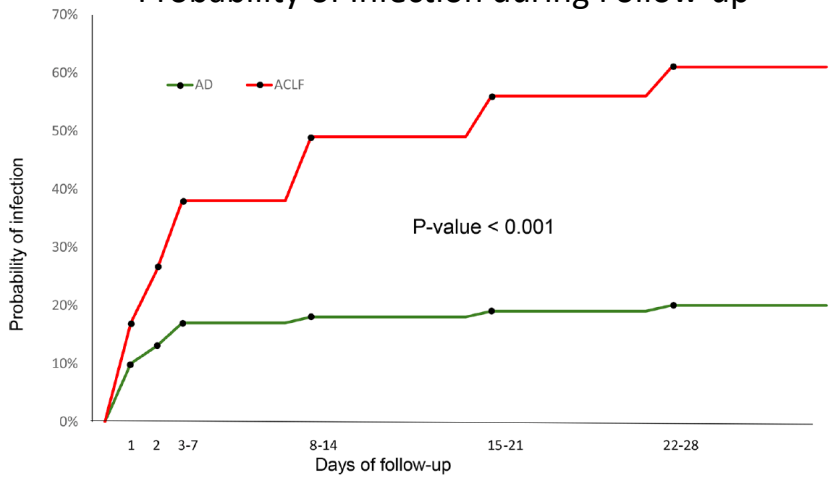




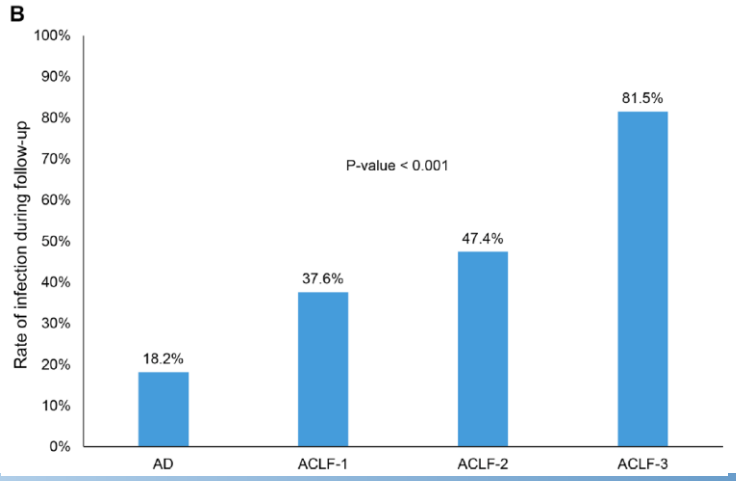
RH Zhao et al. Expert Rev Gastroenterol Hepatol 2018

Transplant-Free Survival in ACLF +/- Bacterial Infections

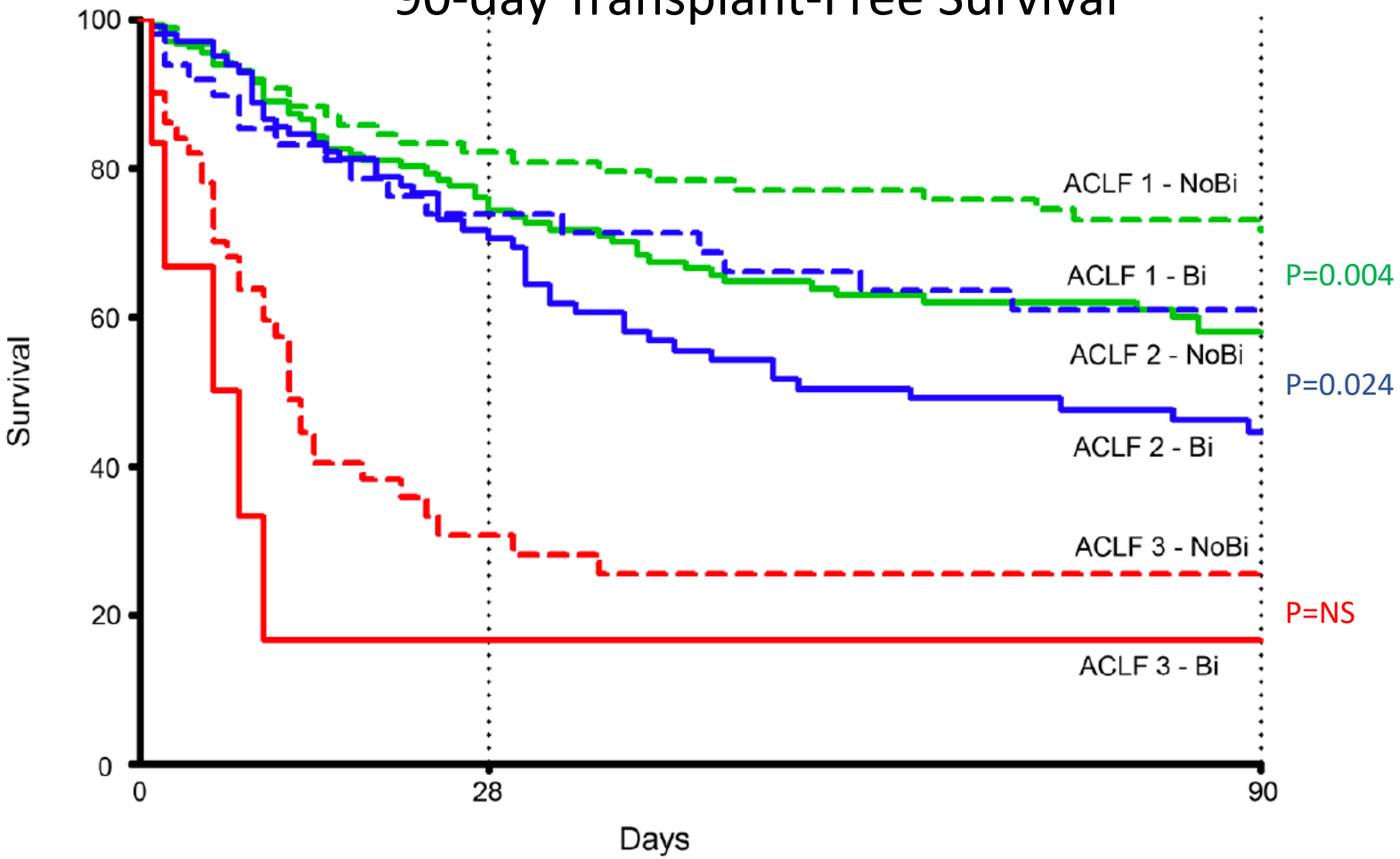
Probability of Infection during Follow-up



Incidence of Infection during Follow-up



90-day Transplant-Free Survival



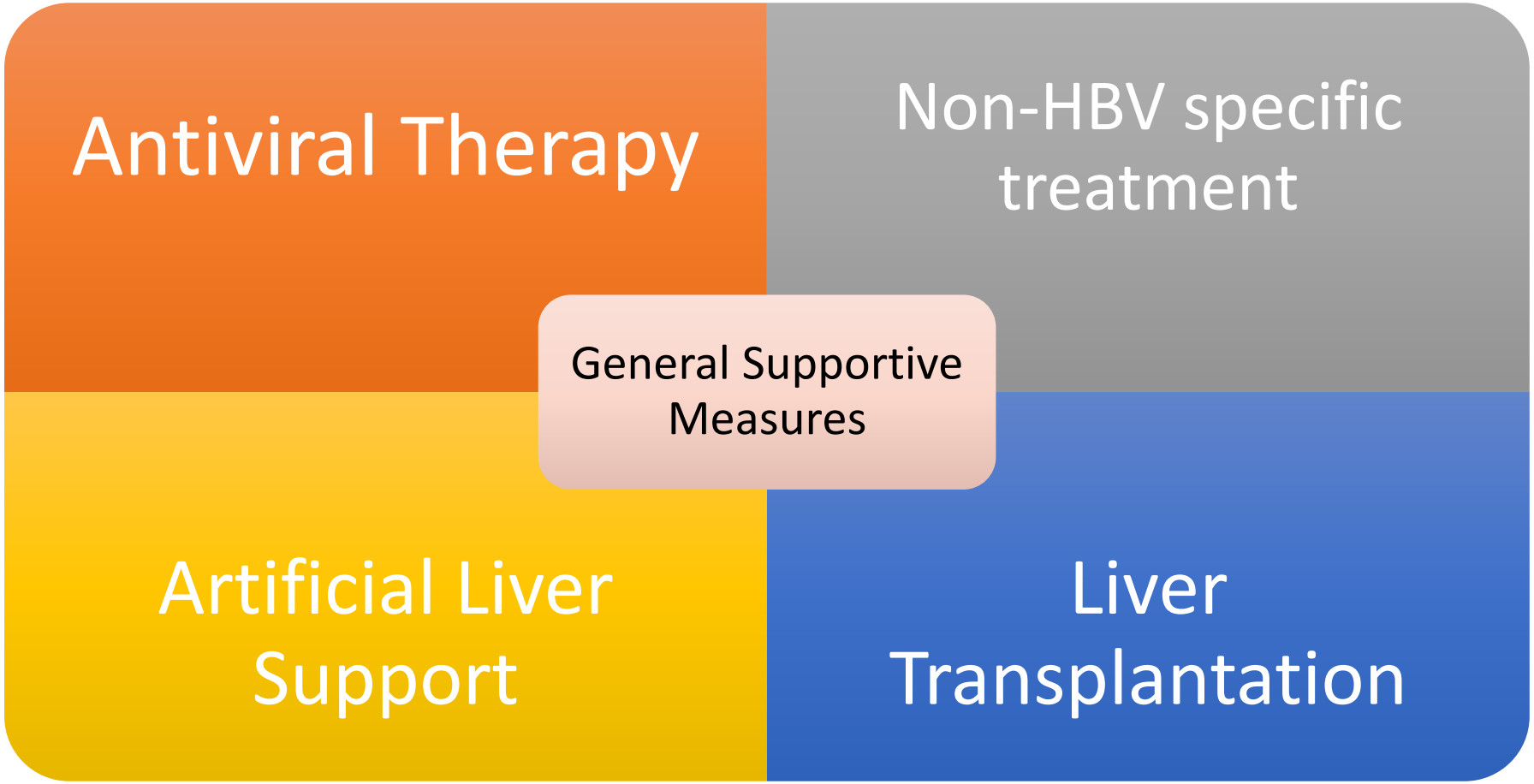
Fernandez J et al. Gut 2018

Diagnosis of Acute Flares of CHB and Difference between Acute Hepatitis B vs. Acute flares of CHB

- Patients may present with acute flares of CHB without knowing their carrier status
  - Severe acute flare may be the first presentation
  - Difficult to differentiate between acute flare of chronic infection and acute hepatitis B

	Acute HBV infection	Acute flares of Chronic Infection
History	Recent at-risk behavior	History of hepatitis/family history
Anti-HBc (qualitatitive)	Positive	Maybe positive (~25%)
Anti-HBc IgM titre	High (>1:1000)	Low if present (<1:1000)
HBeAg/anti-HBe	Positive or negative	Positive or negative
HBV DNA	Lower ($<10^5$ copies/mL)	Higher ($\geq 10^5$ copies/mL)
ALT levels	Very high	Very high
Histology	No chronic changes	Chronic changes
HBsAg at 6 months	Negative	Positive

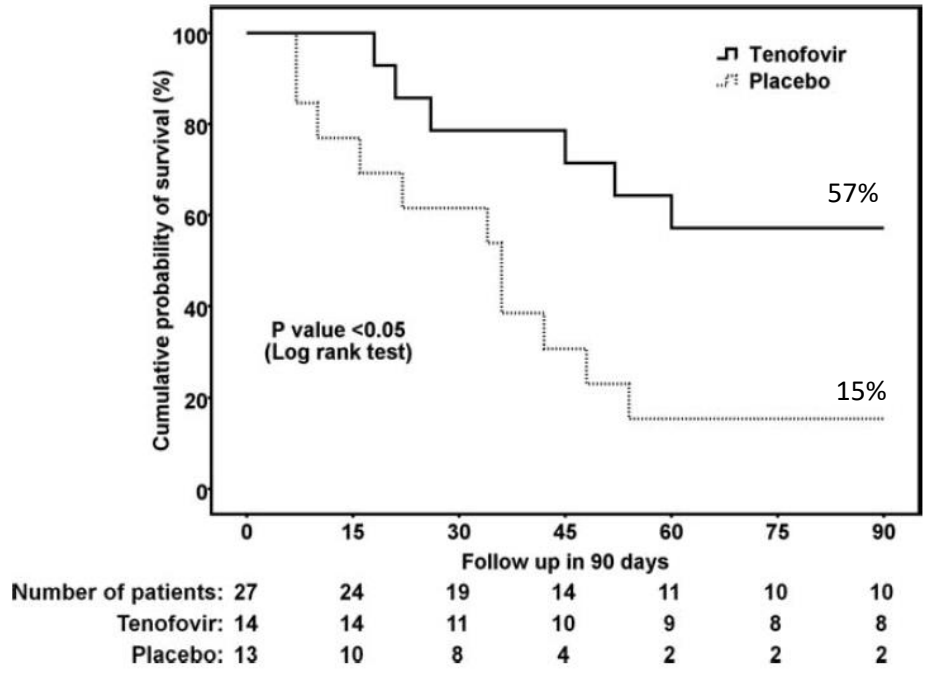
Management of Acute Flares of Chronic Hepatitis B and ACLF



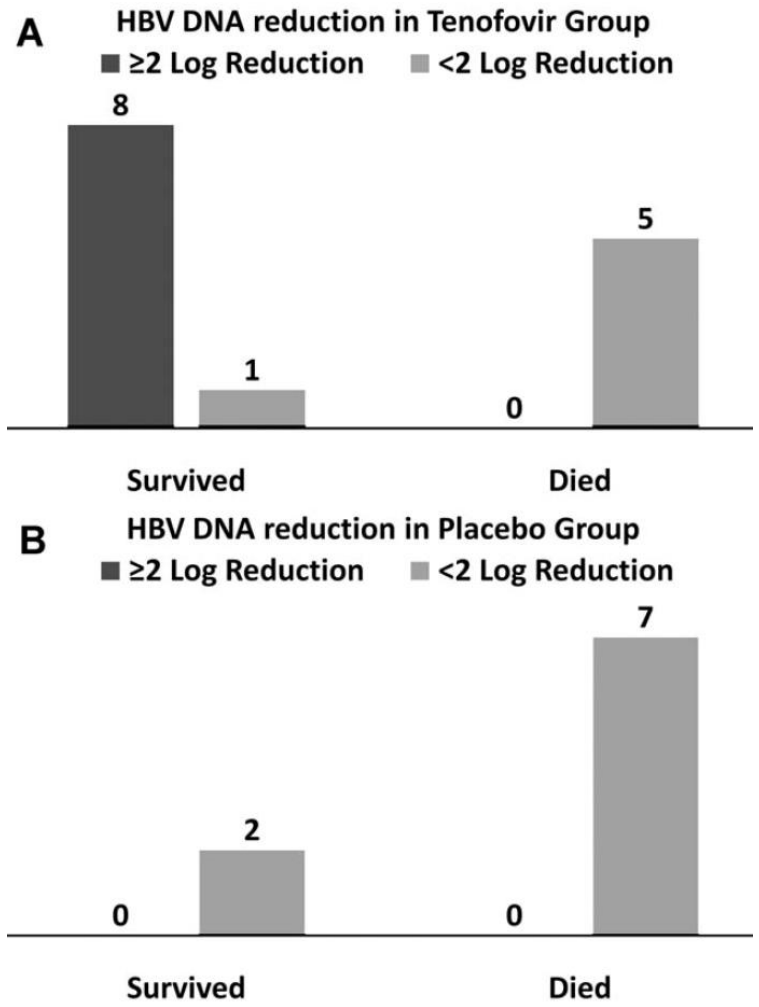
Tenofovir vs. Placebo in Treatment of HBV Flare

Consecutive patients of ACLF due to spontaneous reactivation of CHB were randomized to receive either tenofovir or placebo

INR>1.5; bilirubin >85mmol/L, ascites/encephalopathy

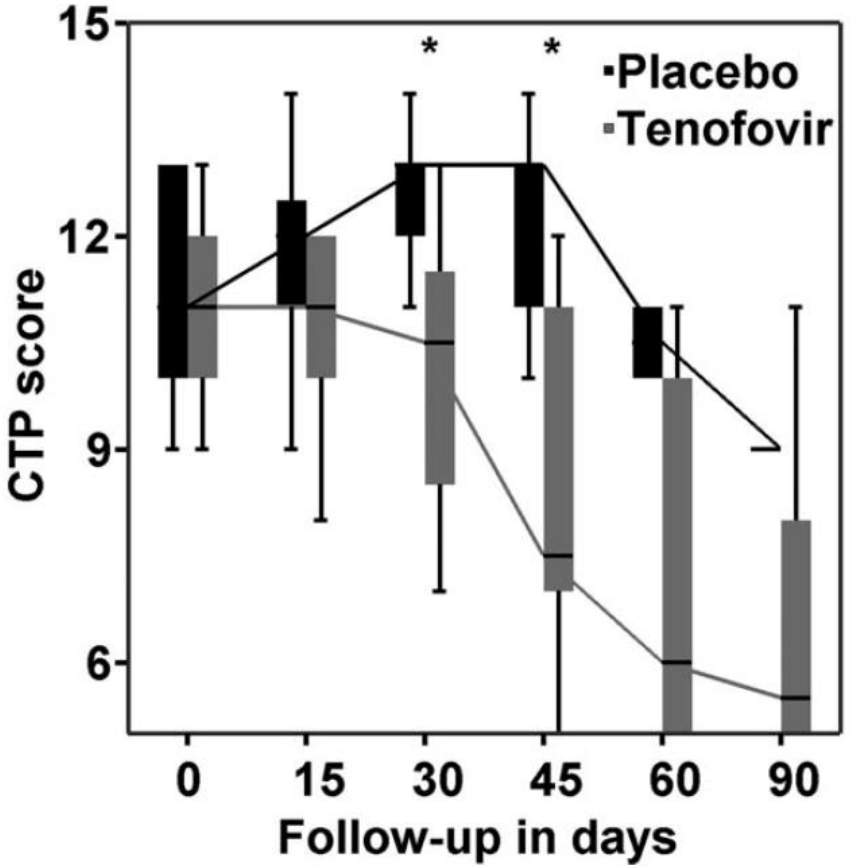


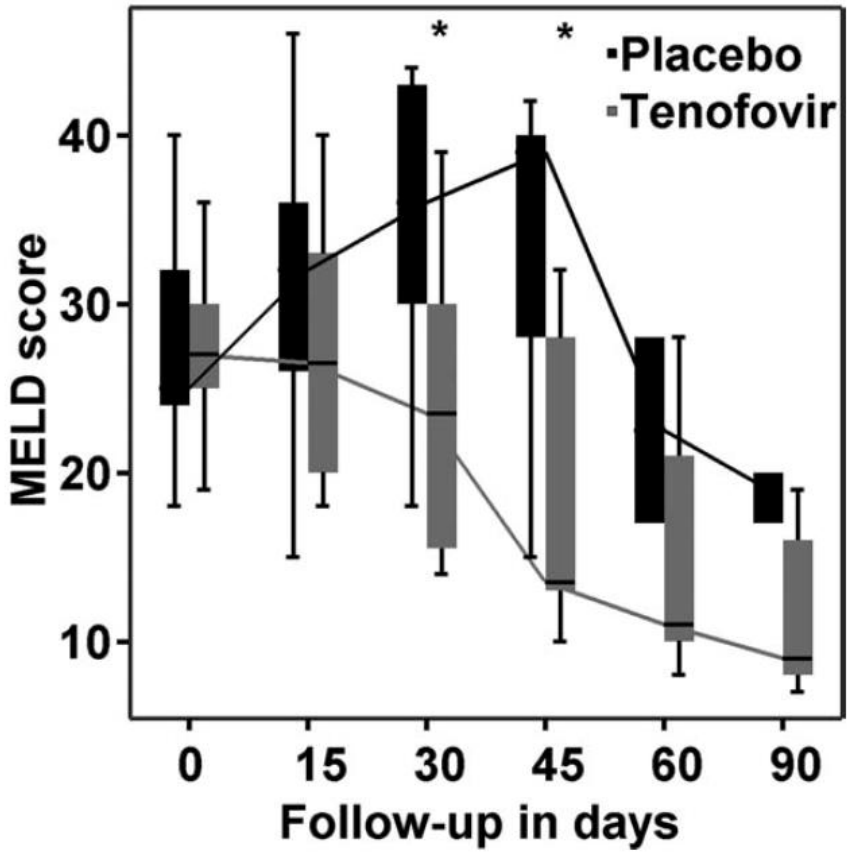
More than 2 log reduction in HBV DNA levels at 2 weeks was found to be an independent predictor of survival



Improvement in Child-Pugh and MELD Scores in Treated Patients

In the surviving patients, there was a significant improvement in the Child-Turcotte Pugh (CTP) and Model for End-stage Liver Disease (MELD) scores

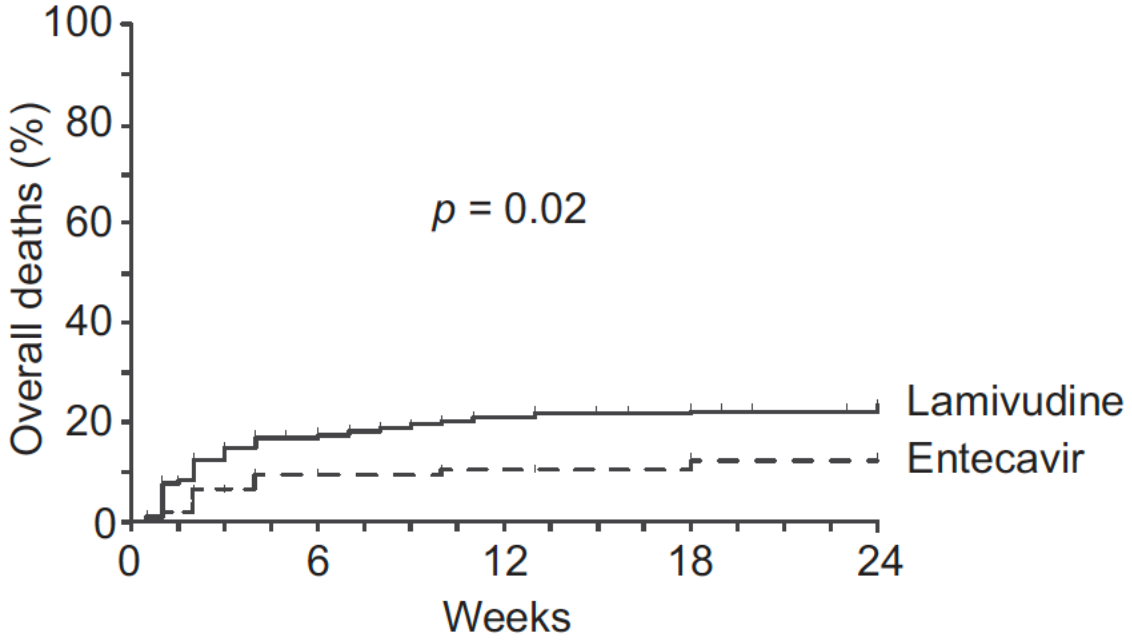


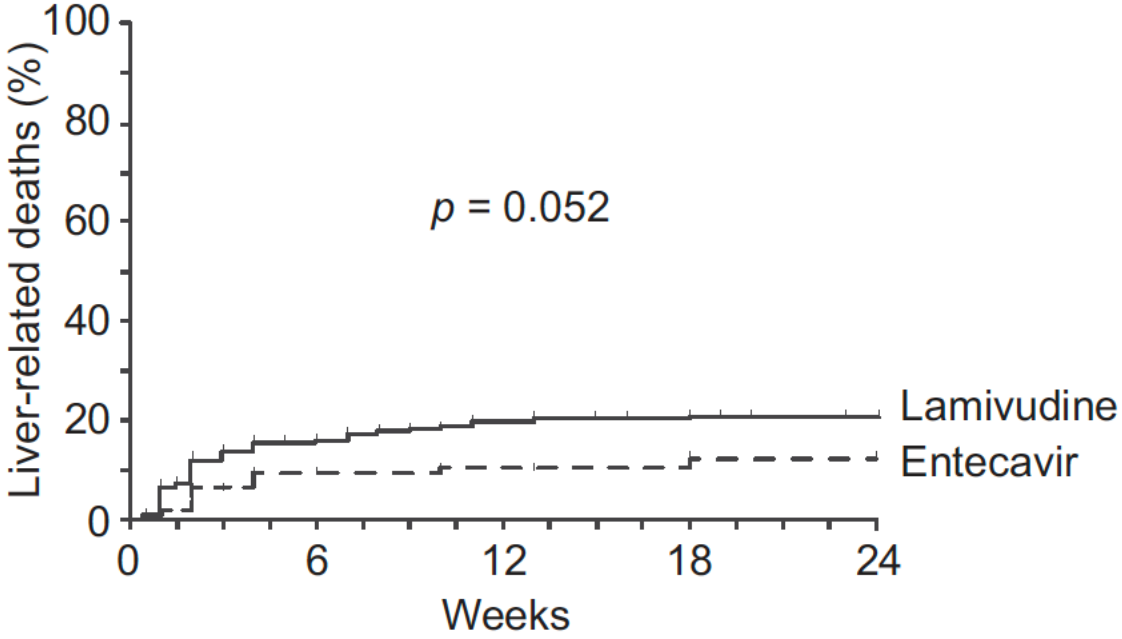


H Garg et al. Hepatology 2011

ETV vs. LAM in Severe Acute Flares of CHB with Decompensation

Consecutive CHB naïve patients with severe acute exacerbation and hepatic decompensation
215 treated with LAM, 107 treated with ETV





Univariate analysis showed LAM had higher rate of overall & liver-related mortality at week 24 than ETV, including patients with ACLF
Multivariate analysis showed MELD scores, ascites, and HE to be independent factors for overall and liver-related mortality at week 24
ETV or LAM treatment was not an independent factor for mortality in all patients or patients with ACLF

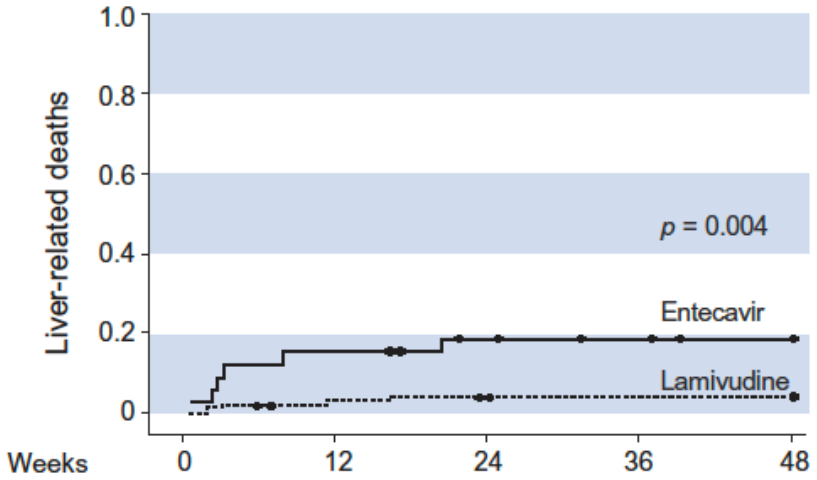
ETV Treatment in Severe Acute Flares of CHB

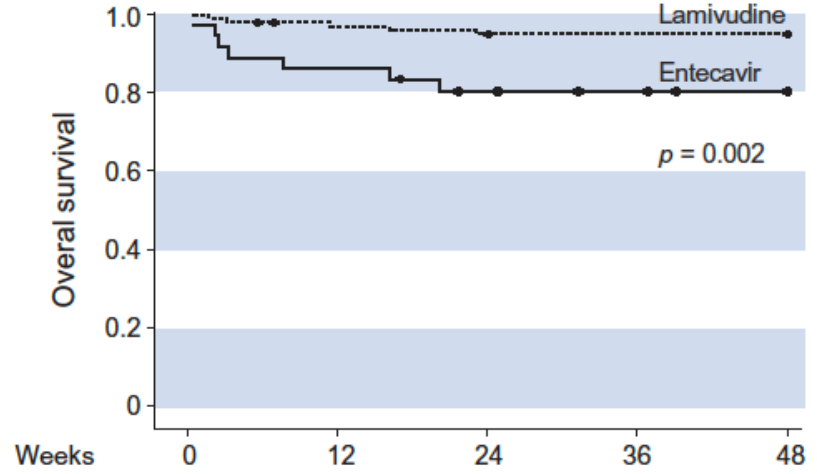
Table 1. Baseline characteristics of patients with severe acute exacerbation of chronic hepatitis B on entecavir and lamivudine treatment.

Characteristics	Entecavir (N = 36)	Lamivudine (N = 117)	*p* Value
Age	51 ± 13 (22-76)	44 ± 14 (16-79)	0.005
Male gender, n (%)	26 (72)	101 (86)	0.049
ALT (IU/L)	1151 ± 724 (194-3020)	1499 ± 841 (181-5430)	0.027
Bilirubin (μmol/L)	165 ± 163 (23-754)	163 ± 121 (27-572)	0.94
Albumin (g/L)	36 ± 5 (22-47)	34 ± 5 (18-48)	0.29
Creatinine (μmol/L)	86 ± 31 (55-214)	90 ± 50 (37-558)	0.73
INR	1.58 ± 0.74 (1.03-4.15)	1.59 ± 0.43 (0.97-3.19)	0.95
Platelet count (×10⁹/L)	174 ± 89 (35-425)	144 ± 57 (17-303)	0.071
HBeAg positive, n (%)	13 (36)	55 (47)	0.25
Anti-HBe positive, n (%)	20 (56)	52 (44)	0.24
HBV DNA (log copies/ml)	7.29 ± 2.08 (2.00-11.33)	7.56 ± 1.62 (2.00-10.30)	0.42
Cirrhosis, n (%)	5 (14)	25 (21)	0.32
Time from presentation to starting antiviral drugs (days)	2.9 ± 2.8 (0-9)	2.8 ± 4.1 (0-29)	0.90

Patient	Gender/Age	Treatment	Cirrhosis	Baseline ALT (IU/L)	Bilirubin (μmol/L)	INR	MELD score	HBV DNA (log copies/ml)	Survival (Weeks)	Cause of death
1	M/70	Entecavir	No	2290	325	3.95	35	8.68	0.6	Liver failure
2	M/48	Entecavir	No	282	194	1.09	18	3.51	16.3	Pancreatic cancer
3	M/61	Entecavir	No	285	601	2.07	28	3.33	2.4	Liver failure
4	F/55	Entecavir	No	2180	251	4.15	33	8.91	3.3	Liver failure
5	F/70	Entecavir	No	1105	331	3.08	32	8.37	2.1	Liver failure
6	M/57	Entecavir	Yes	908	55	1.27	14	9.83	7.7	Liver failure
7	M/52	Entecavir	Yes	377	89	1.24	15	7.30	20.3	Liver failure
8	F/79	Lamivudine	Yes	278	102	2.17	22	6.26	16.3	Liver failure
9	M/45	Lamivudine	No	2210	205	1.88	23	7.42	3.1	Liver failure
10	F/56	Lamivudine	Yes	1552	322	2.09	26	9.43	1.9	Liver failure
11	M/42	Lamivudine	No	1513	166	3.19	41	9.32	11.4	Liver failure
12	M/44	Lamivudine	No	2100	195	1.93	23	8.15	23.3	Acute myeloid leukemia

ALT, alanine aminotransferase; HBV, hepatitis B virus; INR, international normalized ratio; MELD, Model for End-stage Liver Disease.





VWS Wong et al. J Hepatol 2011

Could there be a possible cause for mortality associated with ETV use?

Severe Lactic Acidosis During Treatment of Chronic Hepatitis B with Entecavir in Patients with Impaired Liver Function

Christian M. Lange, Jörg Bojunga, Wolf Peter Hofmann, Katrin Wunder, Ulrike Mihm, Stefan Zeuzem, and Christoph Sarrazin

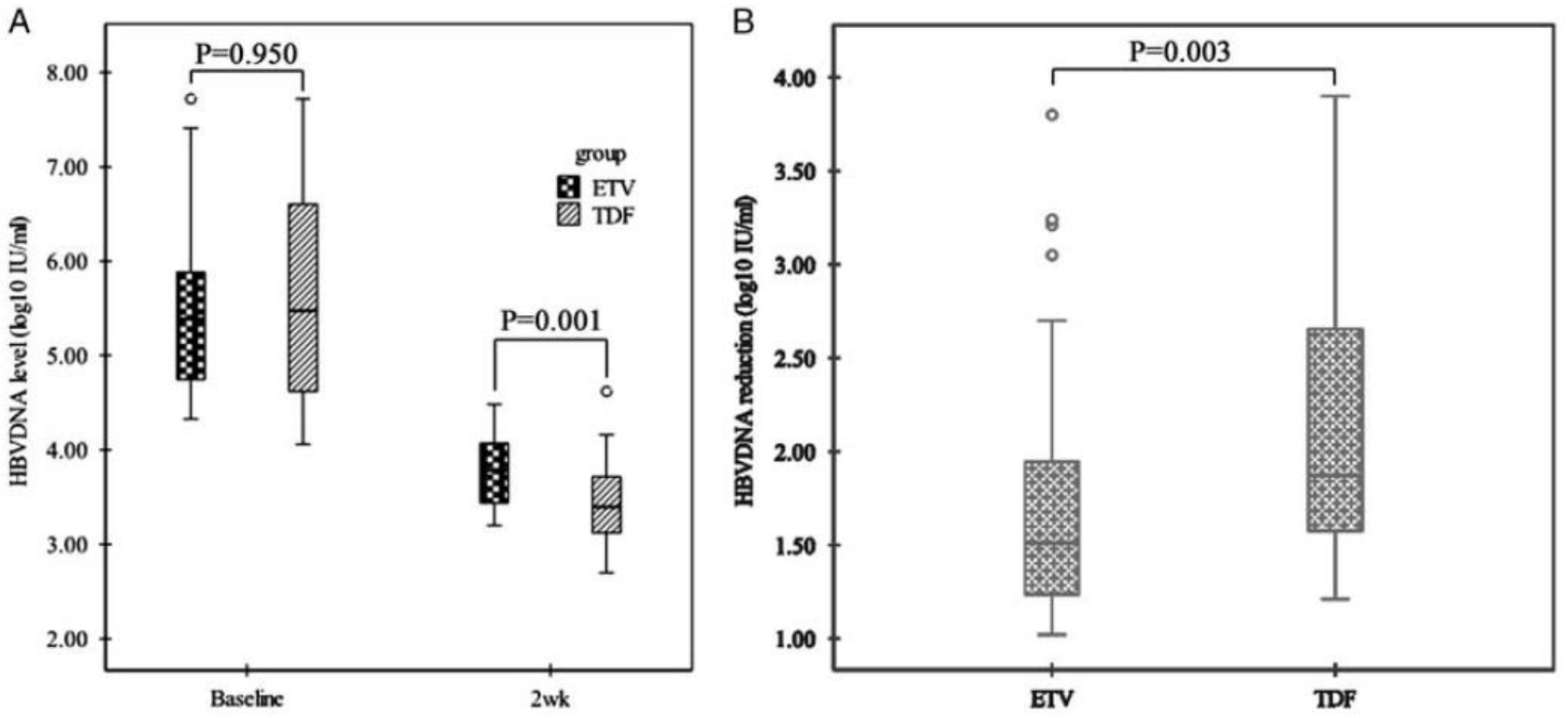
- 16 patients with HBV cirrhosis treated with ETV
  - 5 developed lactic acidosis
  - Occurred 4-240 days after treatment
  - 1 death
- The MELD score (and not CPS) correlated with development of lactic acidosis
  - All had MELD >18
  - All had impaired CrCl
- Important to dose-adjust for renal impairment

Lange CM et al. Hepatology 2009

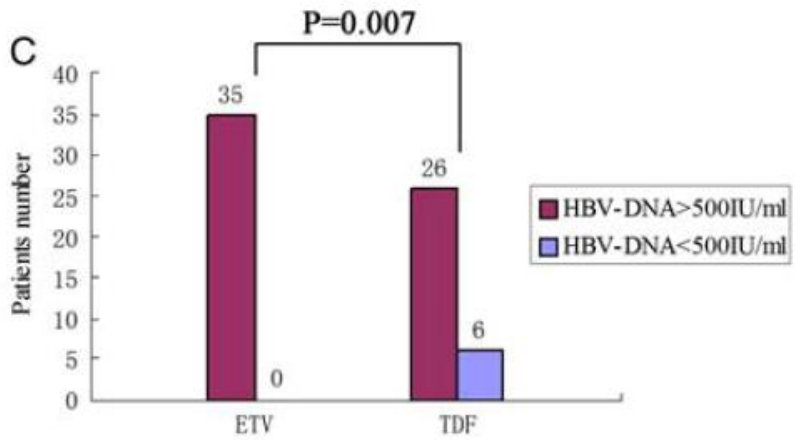
TDF vs. ETV for HBV-related ACLF (Genotype B&C)

67 consecutive HBV-ACLF patients divided into TDF (n=32) and ETV group (n=35)

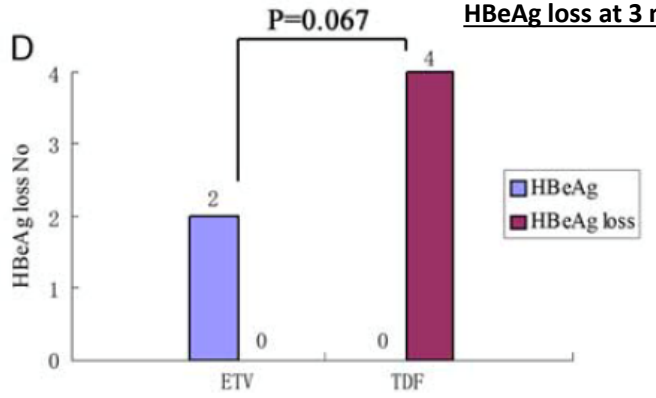
HBV DNA at baseline and 2 weeks



HBV-DNA undetectability rate at 2 weeks

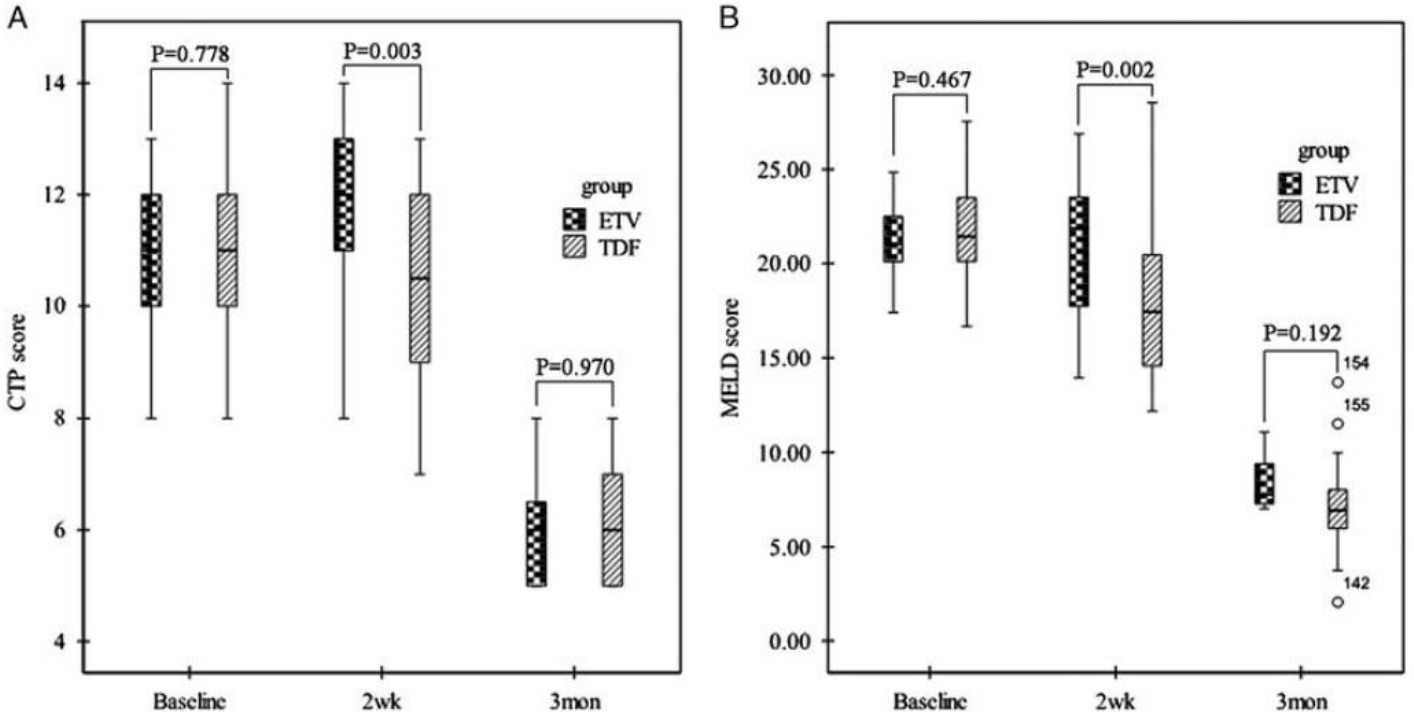


HBeAg loss at 3 month

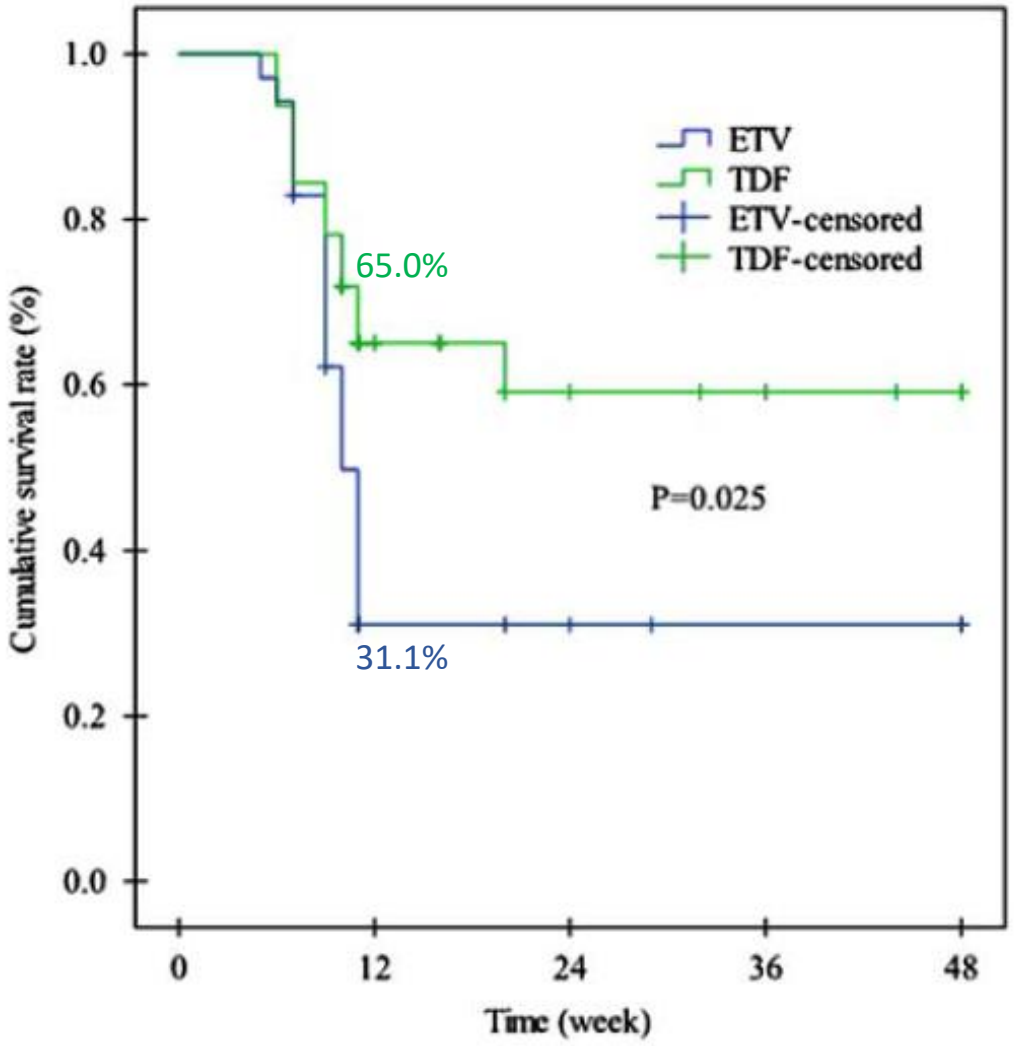


YM Wan et al. J Clin Gastroenterol 2019

CTP, MELD, and Survival in TDF vs. ETV for HBV-ACLF



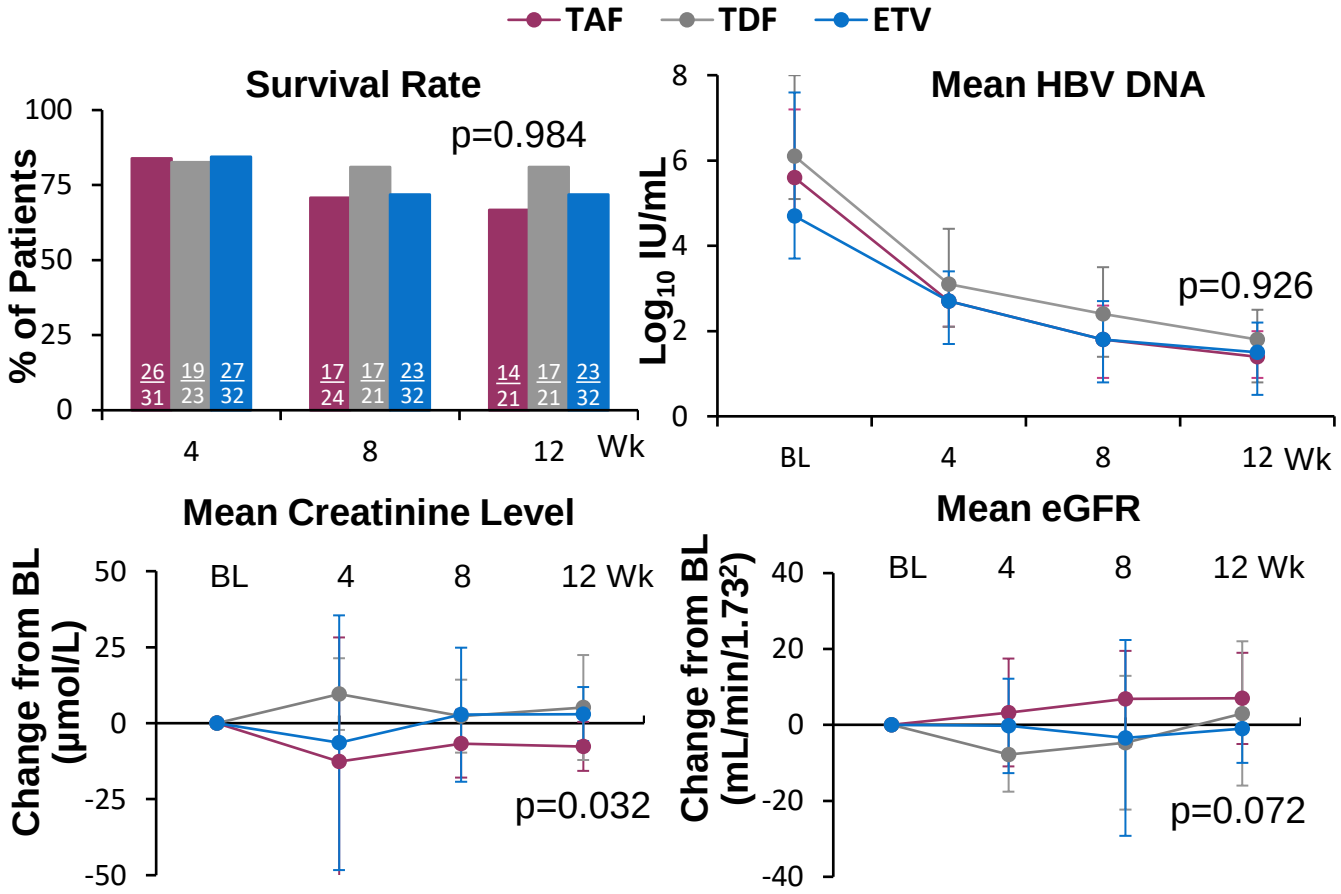
The white blood cell count (HR, 2.726; P=0.000), and HBV-DNA reduction (HR, 0.266; P=0.013) at 2 weeks were independent predictors for mortality



Effectiveness and Safety of TAF in Treatment-Naïve Patients with HBV-related ACLF in China

A prospective clinical study of 12-week TAF, TDF or ETV treatment in 88 treatment-naïve patients with HBV-related ACLF in the third affiliated hospital in China

Baseline Demographics	TAF (n=33)	TDF (n=23)	ETV (n=32)
Mean age, y (SD)	43.0 (11.2)	23.7 (8.3)	43.0 (9.9)
Male, n (%)	30 (91)	20 (87)	29 (91)
HBeAg-positivity, n (%)	19 (58)	12 (52)	10 (31)
Mean HBV DNA, log_{10} IU/mL (SD)	5.5 (1.6)	6.1 (1.9)	4.7 (2.9)
Mean ALT, IU/mL (SD)	689 (661)	1,008 (900)	712 (841)
Mean AST, IU/mL (SD)	612 (671)	729 (721)	430 (435)
Mean eGFR, mL/min/1.73m^2 (SD)	102.9 (26.7)	109.5 (29.7)	103.8 (25.7)



- No treatment-related AEs were observed in study subjects

In patients with HBV-related ACLF in China, TAF, TDF and ETV were well-tolerated with comparable effectiveness

Acute Flares of CHB – To Treat or Not To Treat

Not Treat

- Potential for HBeAg seroclearance and/or immune control
- Committed to long-term antiviral therapy

Treat

- Improve survival
- Early viral load decline important for survival
- Delay in treatment may lead to futility of therapy
- Prolonged flare may lead to irreversible damage
- Potential for increase hepatocarcinogenesis
- Viral suppression at time of LT increase chance of HBsAg seroclearance after LT
- Treatment is safe

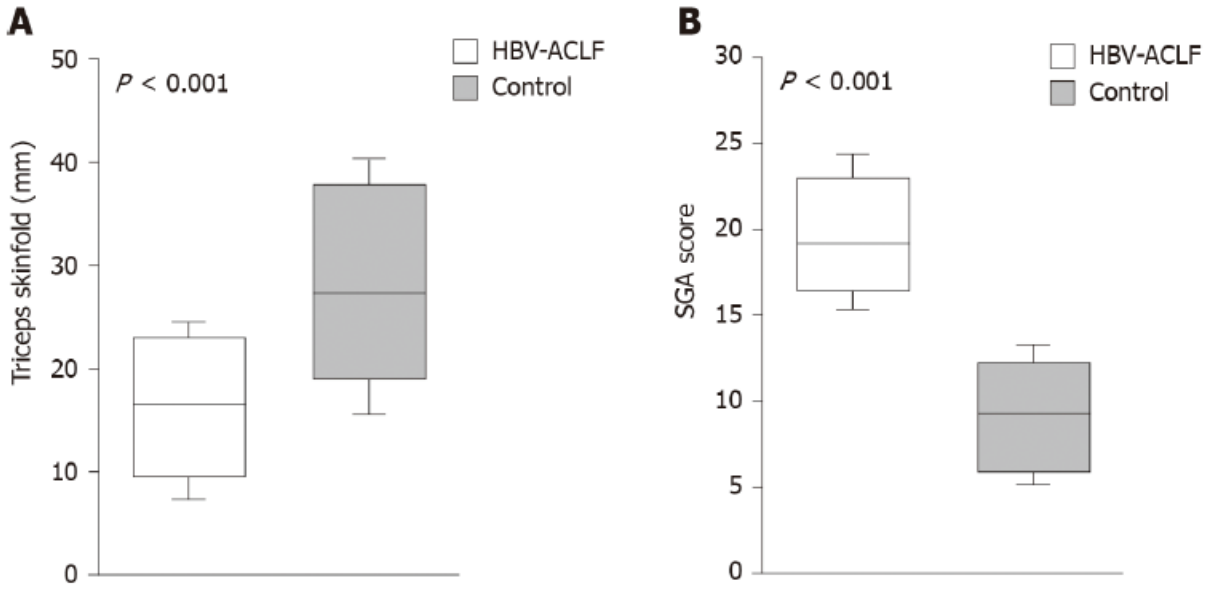
Severe Acute HBV Flares and ACLF Management

- General measures
- Nutritional support
- Treatment of underlying trigger (if present)
  - Early identification
- Organ support
- Treatment of associated complications
- Immunomodulatory (G-CSF)
- Artificial Liver Support Systems (ALSS)
- Liver transplantation

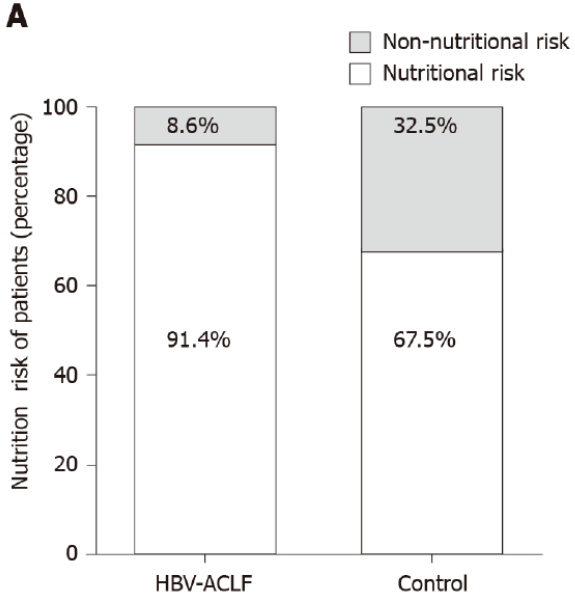
Nutritional Support for HBV-related ACLF

- Most patients with HBV-ACLF will have inadequate nutrient intake and malnutrition at diagnosis or during admission

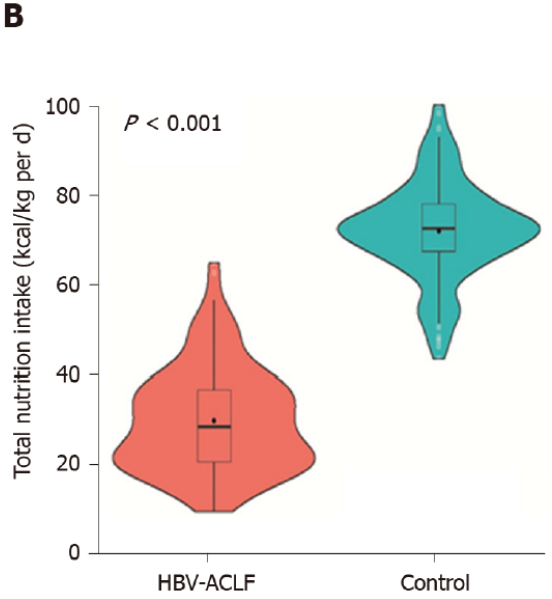
Difference in triceps skinfold thickness and Subjective Global Assessment score



Nutritional Risk



Nutritional Intake

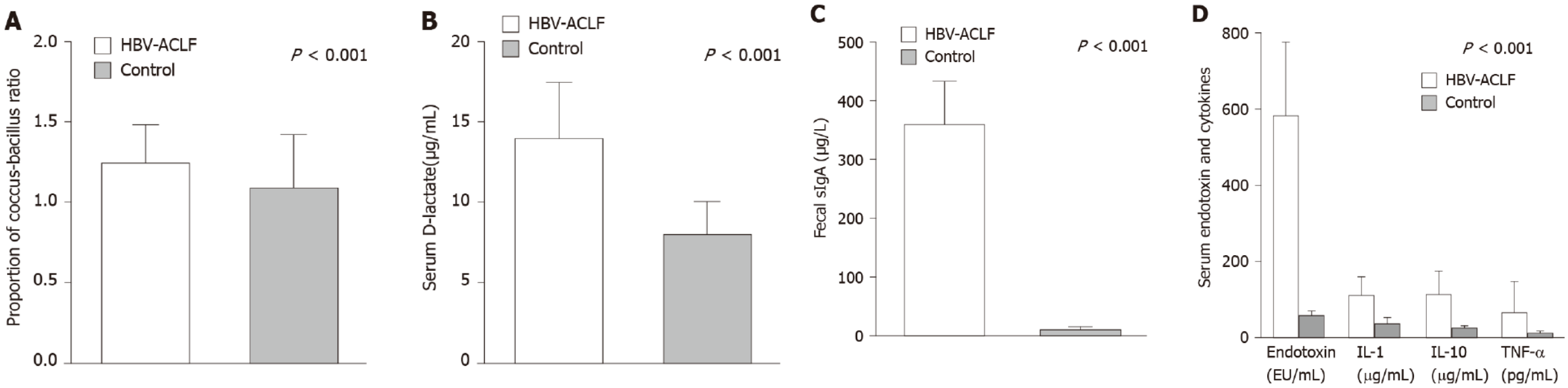


Control = compensated cirrhosis

Gastrointestinal Dysfunction in HBV-related ACLF

- GI dysfunction can occur in liver failure in the early stage
- Portal hypertension, increase abdominal pressure (ascites), and intestinal flora disorders can contribute to malnutrition

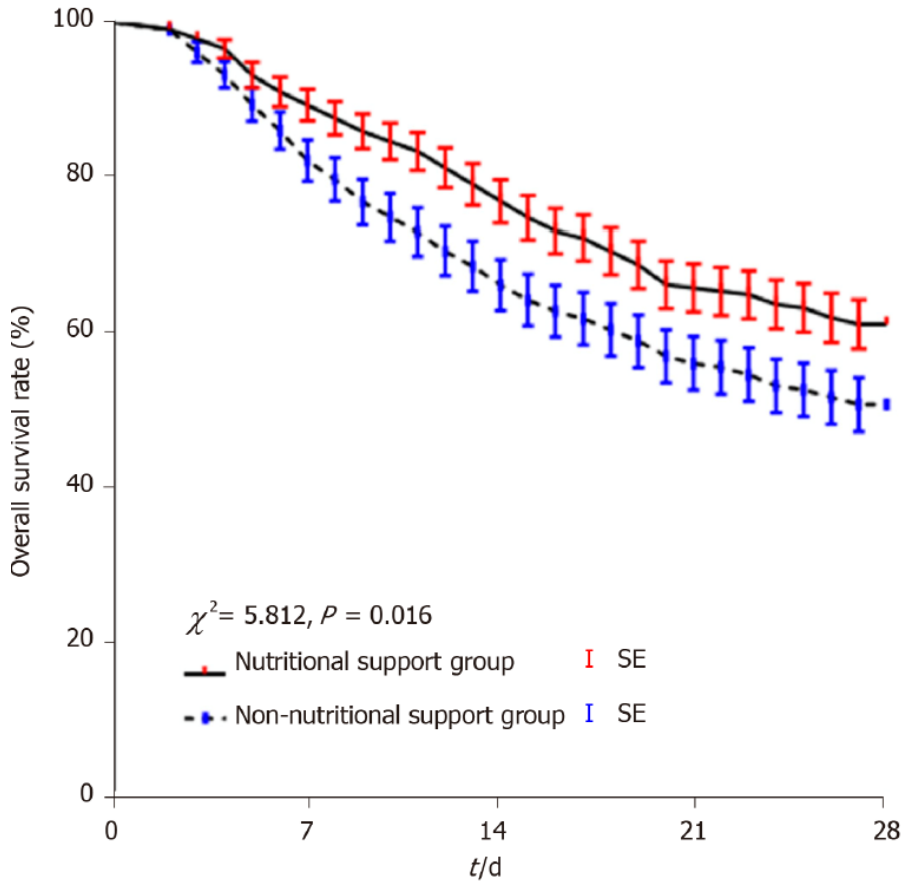
Comparison of biomarkers of the gastrointestinal barrier and inflammation



Control = compensated cirrhosis

Nutritional Support and Short-term Mortality for HBV-related ACLF

Comparison of 28-d mortality between the nutritional support group and the non-nutritional support group



- Individualized and dynamic nutritional support is associated with a better prognosis of 28-d mortality in HBV - ACLF patients
- All patients with HBV-ACLF should be promptly assessed by a dietitian, and be given adequate caloric intake
- Patients should be assessed regularly for adequate intake. Although enteral nutrition is always preferential, parenteral nutrition may be required for supplementation if oral intake is adequate
- Malnutrition, sarcopenia, and frailty may lead to worsening ACLF and worsen LT outcome, increase complications, prolong hospitalization

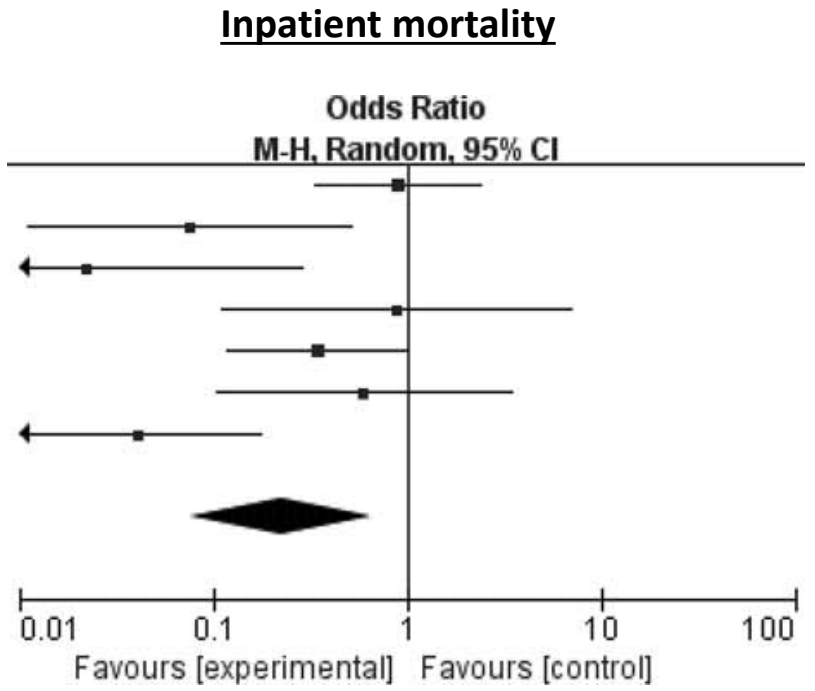
Y Chang et al. World J Gastroenterol 2020

Glucocorticoid Therapy in Severe HBV Flares

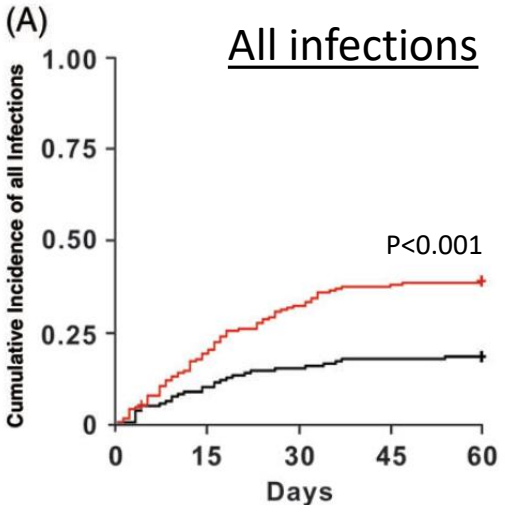
- Anti-inflammatory effect
  - Effective in severe alcoholic hepatitis and autoimmune hepatitis
  - Reduce the immunologically mediated attack on HBV antigens
    - Prevent hepatocyte necrosis
  - Reduces inflammatory cytokines
- Enhance viral replication
  - Reduced risk with more potent NUCs
- Increase risk of sepsis/GI bleeding
  - More effective anti-infective measures

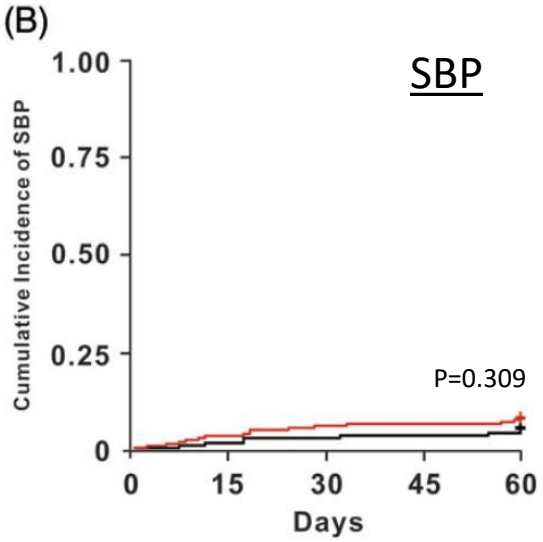
Meta-analysis on Glucocorticoid Therapy vs. Traditional Therapy in Severe HBV Flare

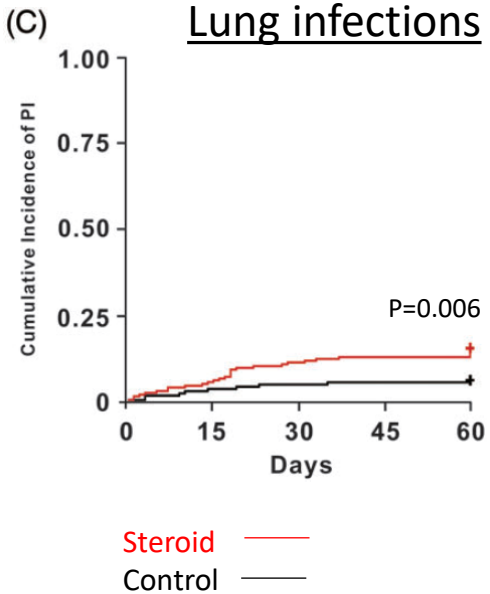
- 3 randomized trials and 5 cohort studies (538 patients)
- Reduction in bilirubin
  - OR: 8.83; 95% CI:14.99 to 2.67; P=0.005
- Shortened PT
  - OR: 31.71; 95% CI: 3.62–59.81; P=0.03
- Lower ascites rate
  - OR: 0.35; 95% CI: 0.18–0.67; P=0.001
- Significantly lower inpatient mortality
  - OR: 0.23; 95% CI: 0.08–0.67; P=0.007
- No difference in ALT levels, HBV DNA



Risk of Infection with Steroid Use in HBV-related ACLF







n (%)	Control group (n = 131)	Steroid group (n = 162)	*P* value
Unidentified infection (body temperature >38 °C)	10 (7.6)	23 (14.2)	0.055
Pulmonary infection	9 (6.9)	30 (18.5)	0.003
Spontaneous bacterial peritonitis	8 (6.1)	15 (9.3)	0.385
Bacteremia	4 (3.1)	7 (4.3)	0.760
Miscellaneous infections[a]	2 (1.5)	11 (6.8)	0.043
Invasive fungal infection and other opportunistic infections	0 (0)	12 (7.4)	0.001

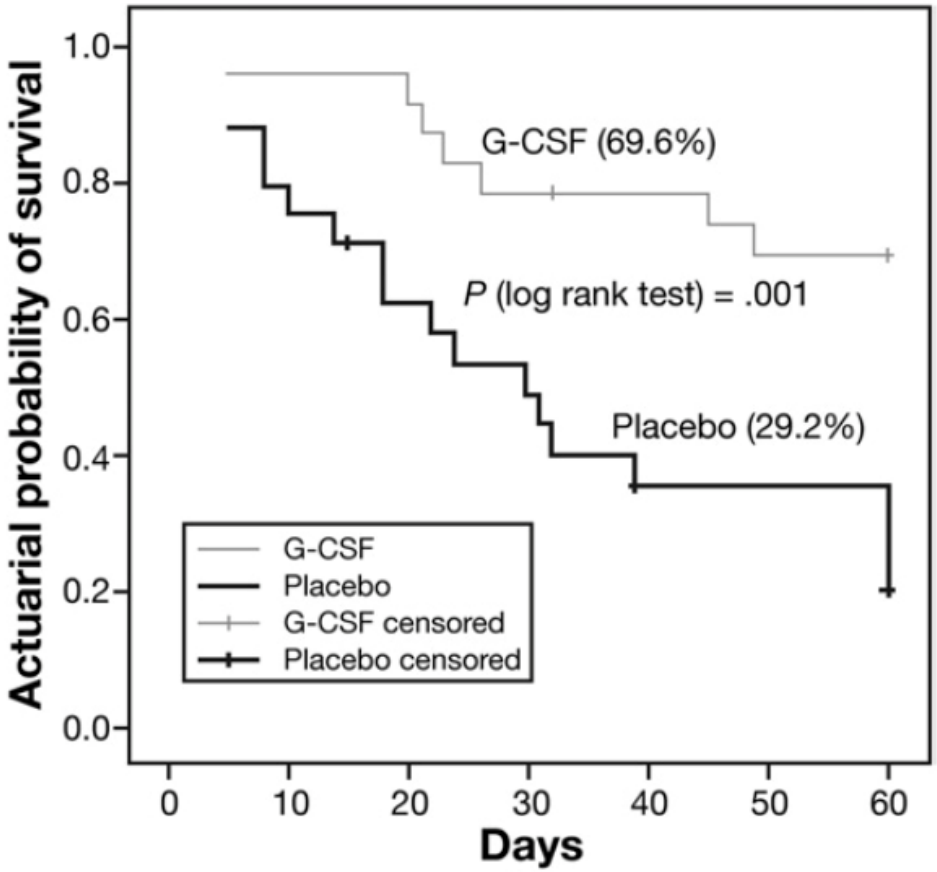
- Infections are significantly increased in steroid use, especially pulmonary infection, invasive fungal infection, and opportunistic infections
- Increase in infection associated with poor outcome, increase mortality, and may offset any benefit from its anti-inflammatory effect

C Huang et al. J Dig Dis 2019

Granulocyte-Colony Stimulating Factor (G-CSF) for ACLF

- After liver injury, bone marrow-derived circulating pluripotent cells contribute to hepatocyte regeneration by providing cytokines and growth factors that promote liver repair
- G-CSF may induce a mobilization of bone marrow CD34+ cells, expression of hepatocyte growth factor and proliferation of hepatic progenitor cells (HPC)
- BM-derived cells may potentially give rise to hepatocytes and cholangiocytes

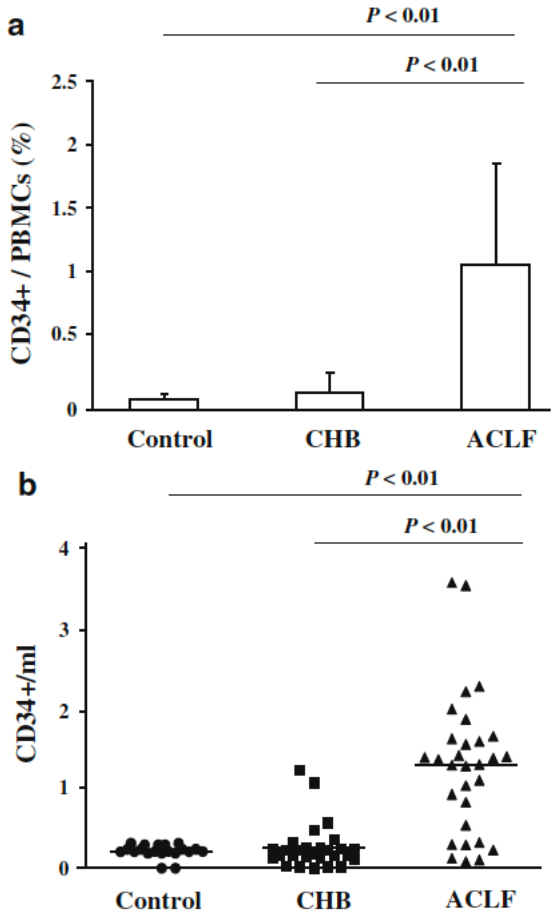
Randomized trial of G-CSF (n=23) vs. placebo (n=24) in ACLF



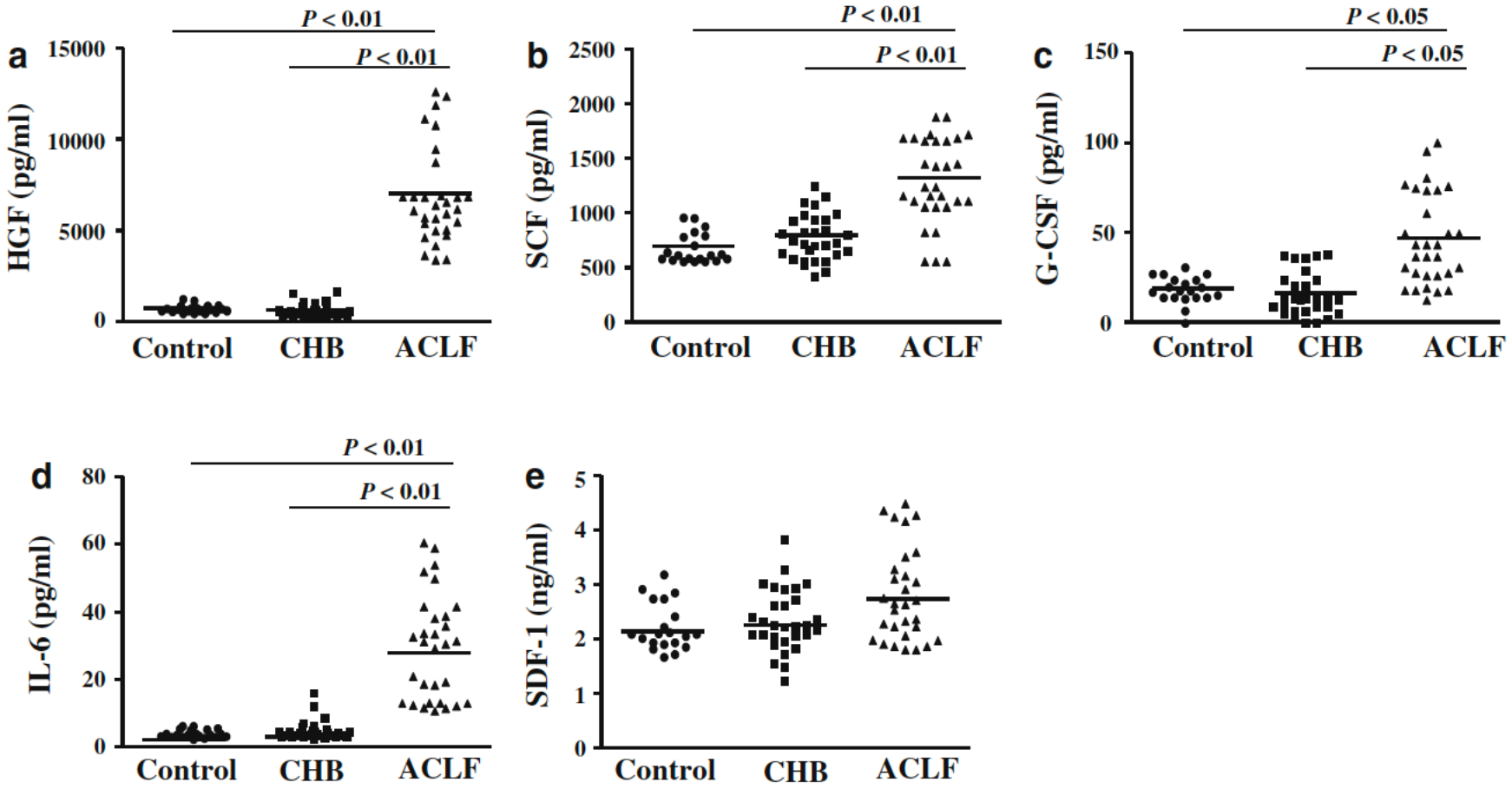
V Garg et al. Gastroenterology 2012

Elevation of CD34+ HSCs & Cytokines in HBV-Related ACLF Patients

Elevation of CD34+ HSCs in the peripheral blood in ACLF



Acute-on-chronic liver failure augments the serum level of multiple cytokines



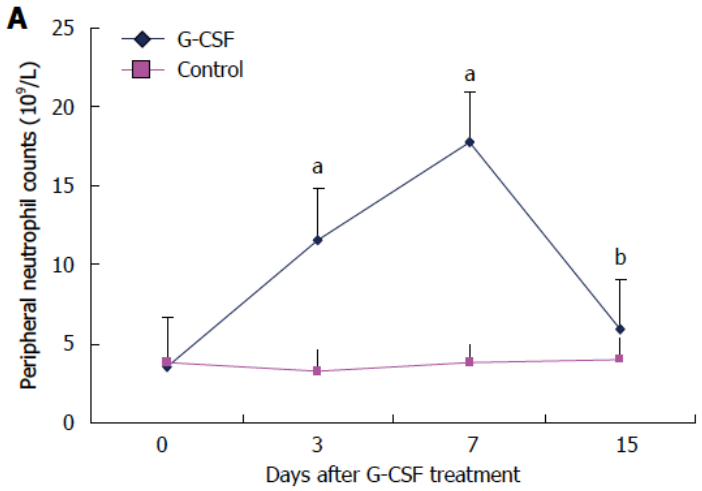
ZH Wan et al. Dig Dis Sci 2013

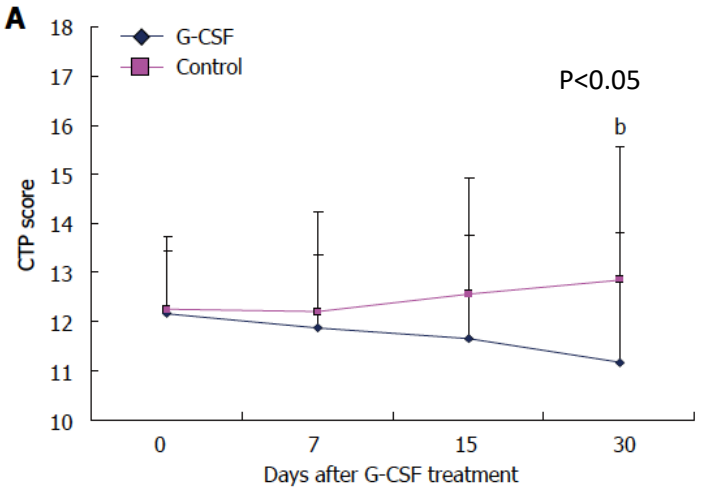
Randomized Double Blind Controlled Trial of G-CSF in HBV-related ACLF

55 HBV-related ACLF randomized to 2 groups
(1) G-GCSF + SMT
(2) Control (SMT only)

G-CSF given at 5mcg/kg SC daily for 6 consecutive days

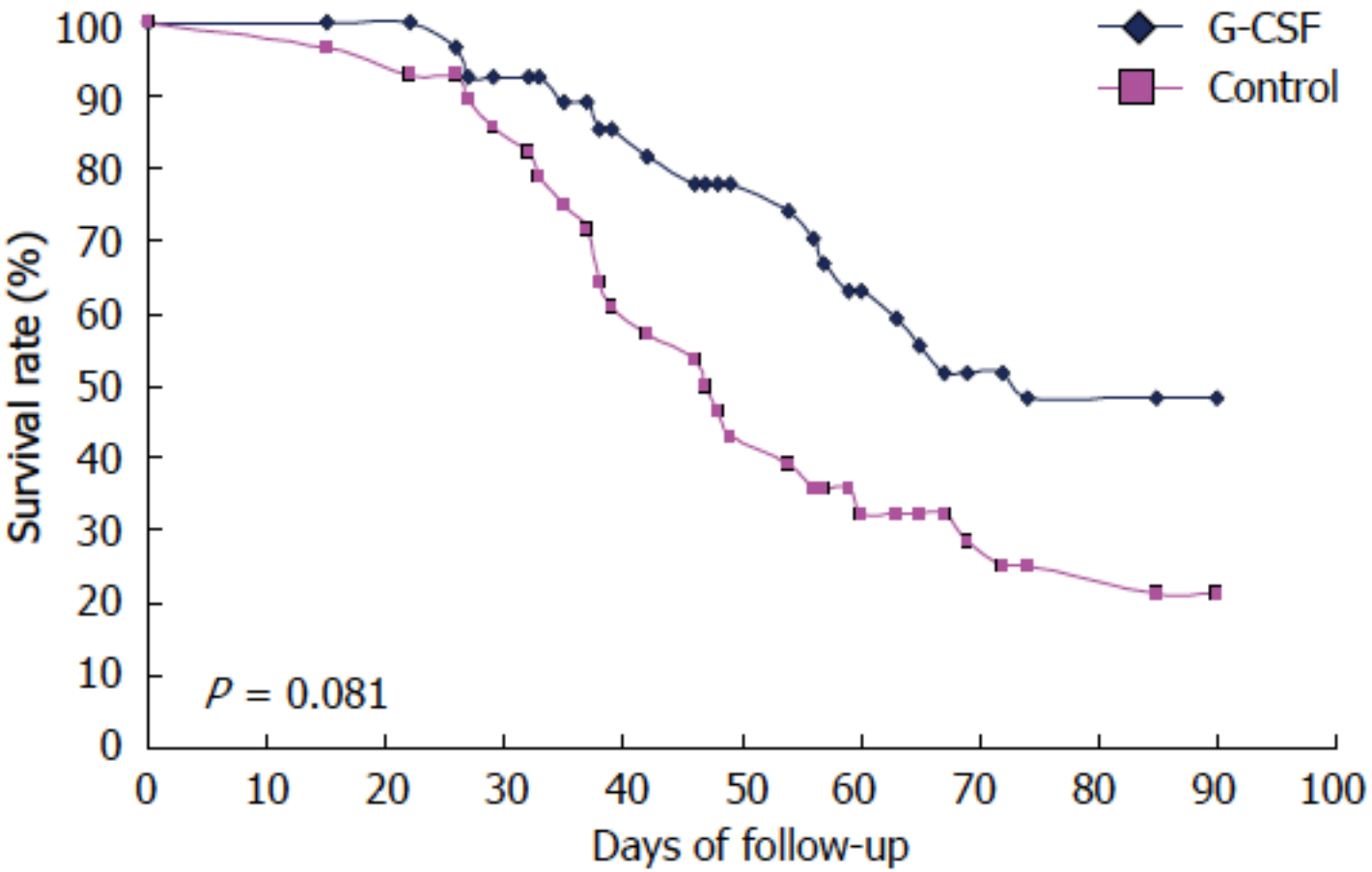
All patients had good tolerance, with some mild S/E (fever, headache, nausea)which resolved after withdrawal of GCSF





XZ Duan et al. World J Gastroenterol 2013

Survival Rates of G-CSF vs. Control in HBV-ACLF



In the G-CSF group, 13 of 27 patients survived, but only 6 of 28 patients survived in the control group (P = 0.0181).

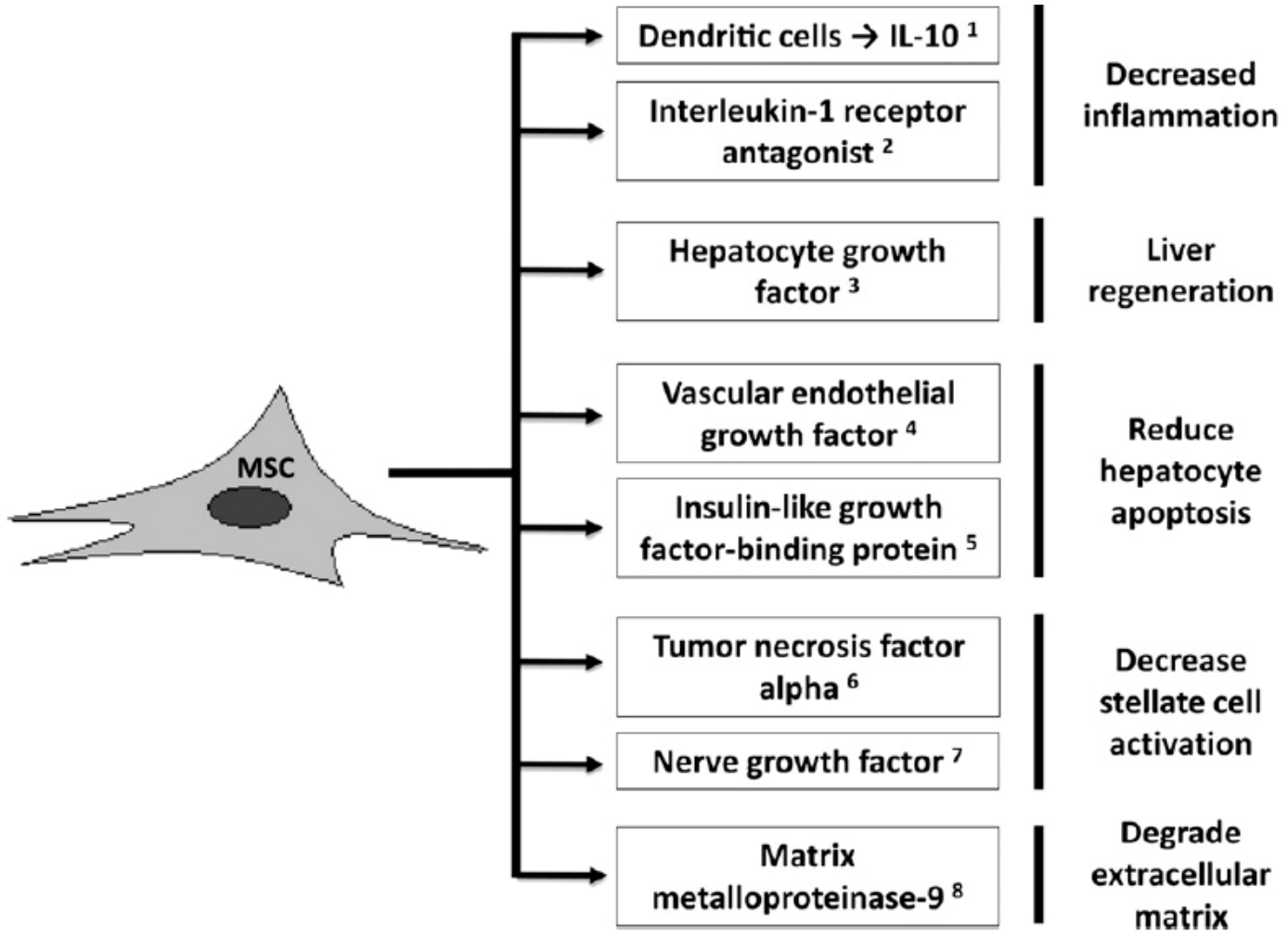
More patients in the control group died of sepsis and HRS compared to those in the G-CSF group (P = 0.027).

XZ Duan et al. World J Gastroenterol 2013

Mesenchymal Stem Cell Therapy for ACLF

- Mesenchymal stem cells (MSC) are multipotent cells that have the potential to differentiate into various types of cells, including hepatocytes

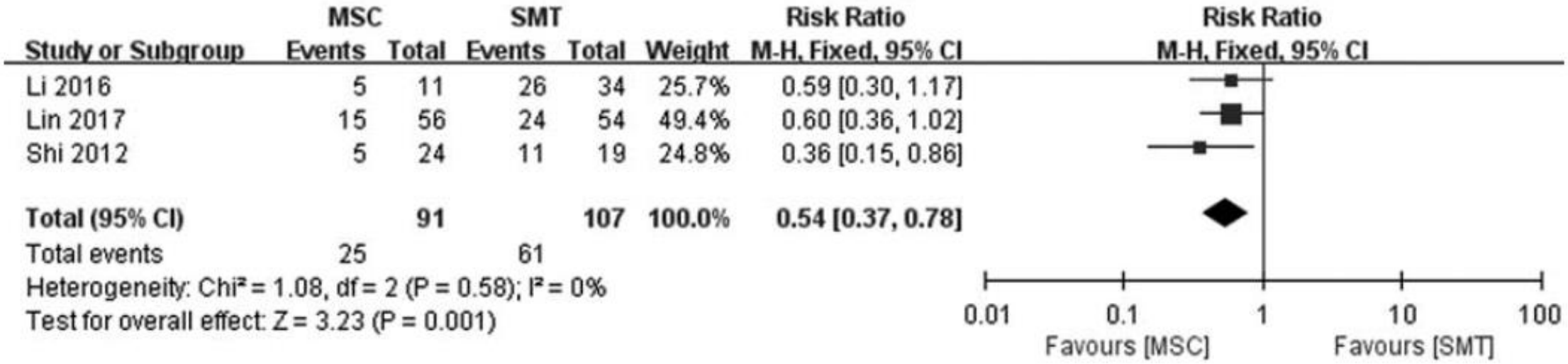
- MSC-derived cytokines can potentially protect liver during injury



RPH Meier et al. Stem Cell Res 2013

Human Mesenchymal Stem Cells for HBV-related ACLF

- 3 studies totally 298 HBV-related ACLF patients
  - 9 treated with MSC, 207 with SMT



Pooled results showed that MSC treatment could significantly reduce the mortality rate

Artificial Liver Support Systems (ALSS)

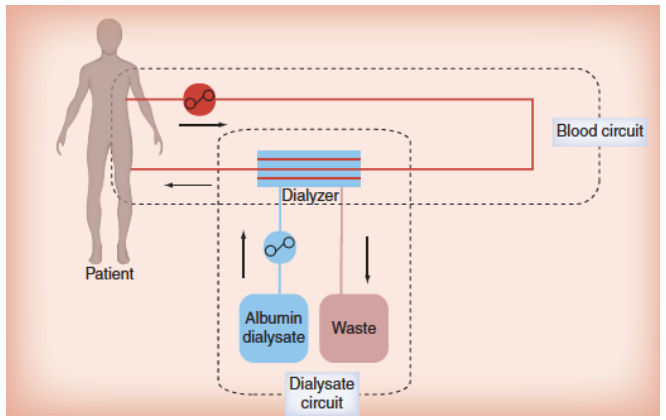
- The ideal liver assist device should support the 3 main liver functions: detoxification, regulation, and synthesis

- The general principles of currently available ALSS is to remove albumin-bound toxins that accumulate in liver failure that contribute to hepatic encephalopathy, HRS, and cardiovascular failure, and to remove water-soluble substances such as ammonia, creatinine, urea, bilirubin, bile acids, cytokines etc.

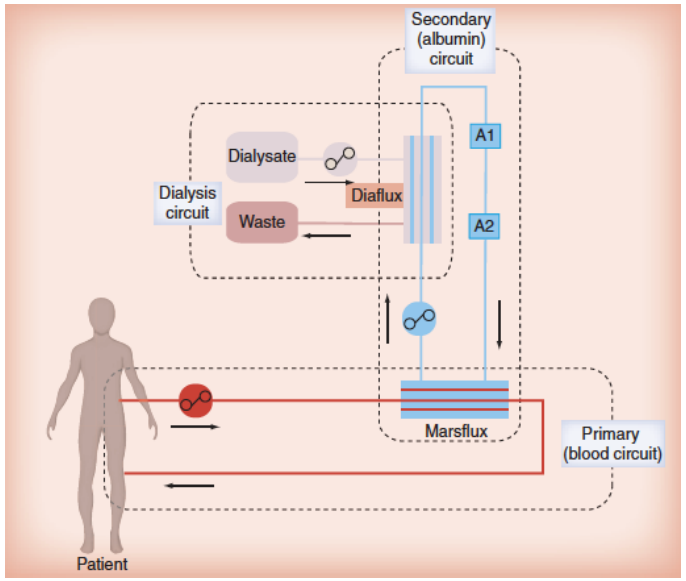
- Conventional extracorporeal procedures such as continuous veno-venous hemodiafiltration (CVVHDF) are highly effective in removal of small, water-soluble toxins such as ammonia and urea, but cannot eliminate large and/or protein-bound molecules

Artificial Liver Support Systems (ALSS)

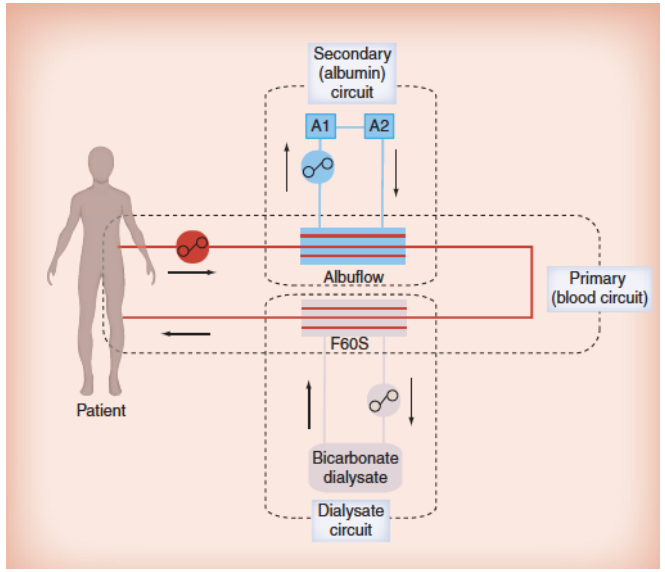
- Plasma exchange/high volume plasmapheresis
  - Patient's plasma removed by plasma filtration and replaced by FFP
- Albumin dialysis



Single-pass albumin dialysis (SAPD)



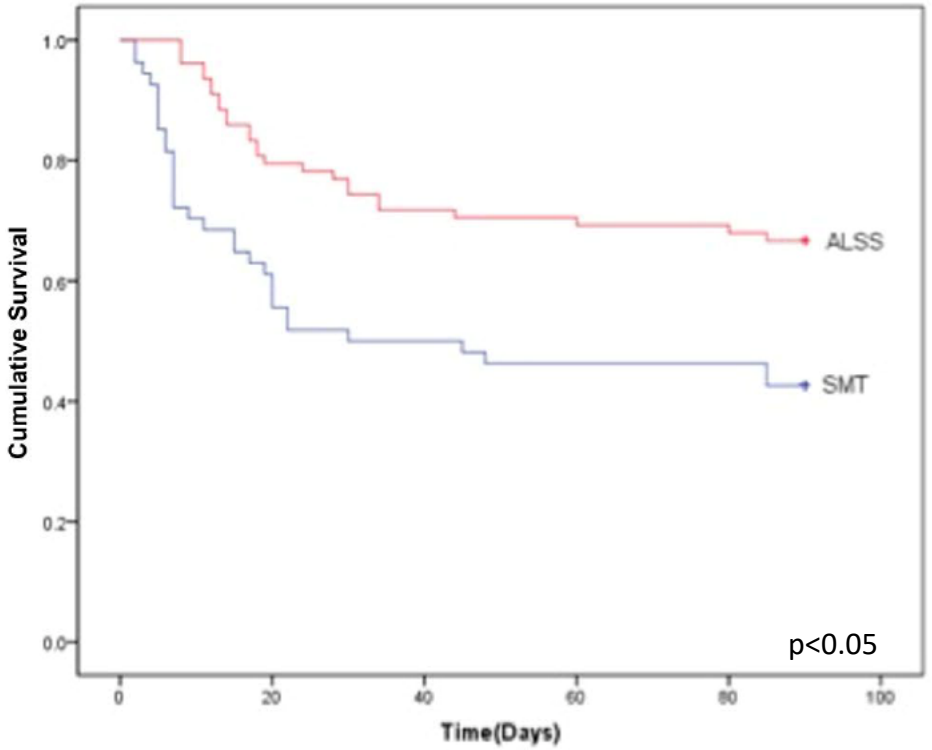
Molecular adsorbents recirculatory system (MARS)



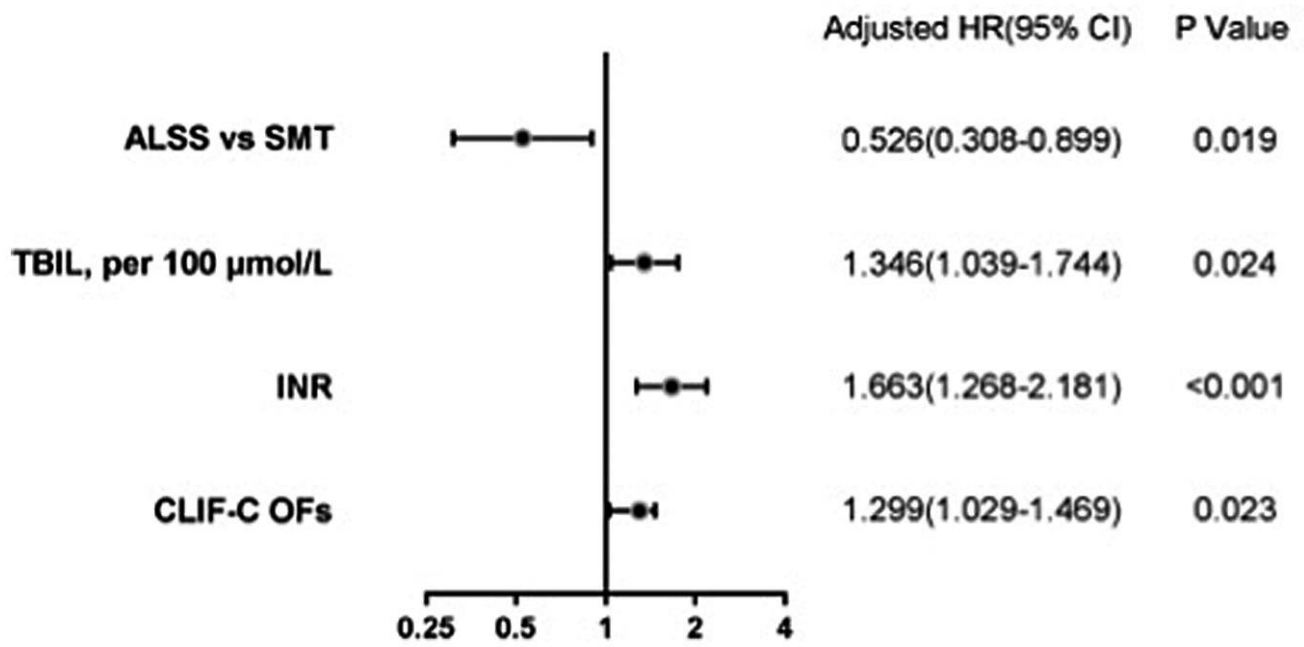
Fractionated Plasma Separation and Adsorption (FPSA, Prometheus)

Artificial Liver Support System in HBV-ACLF

Retrospective study: 132 patients with HBV-ACLF: SMT (54 patients) and ALSS (78 patients)
63 PE, 10 hemofiltration + PE. 5 PE + DPMAS (double plasma molecular adsorption system)



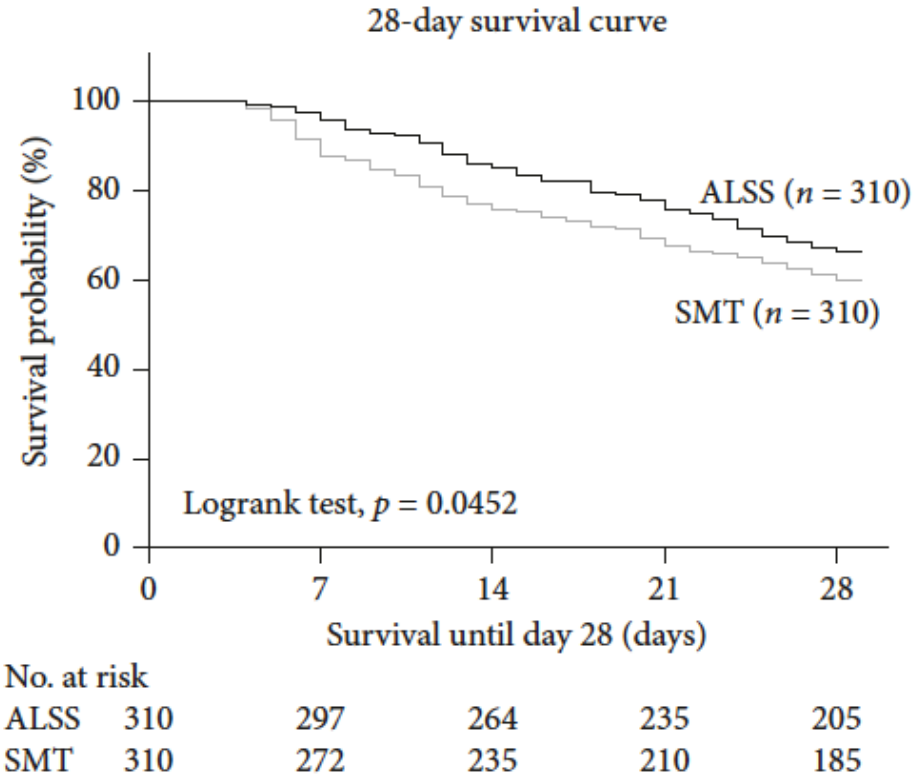
Multivariate analysis of prognostic factors associated with 90-day mortality

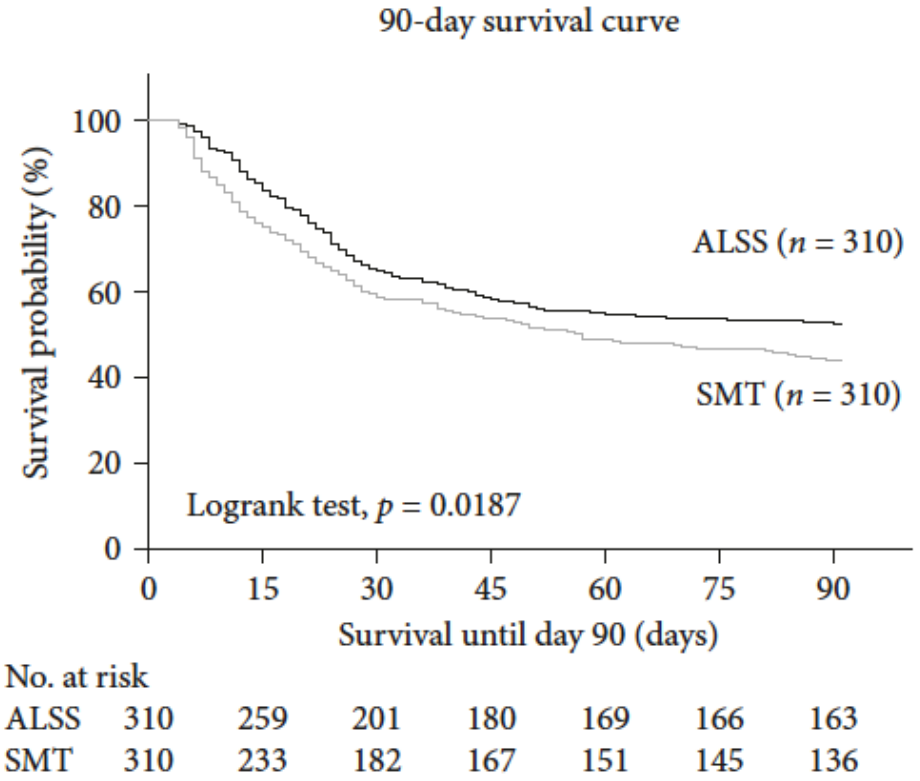


H Liu et al. Artif Organs 2020

Artificial Liver Support System in HBV-ACLF

Retrospective Nationwide Study – HBV-ACLF
790 patients: 412 SMT only + 378 SMT + ALSS
PSM generated 310 pairs and eliminated the baseline differences between the two groups

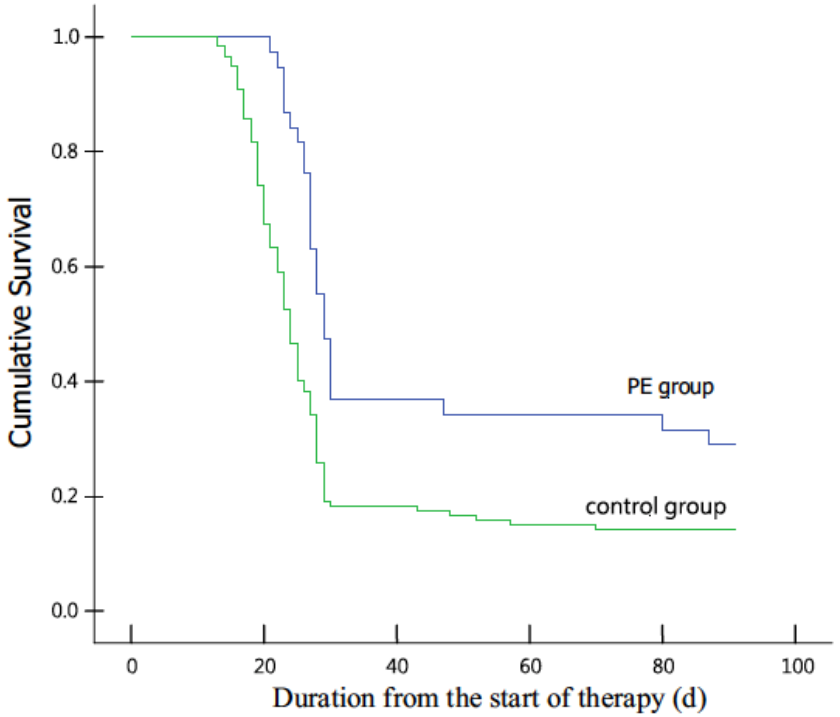




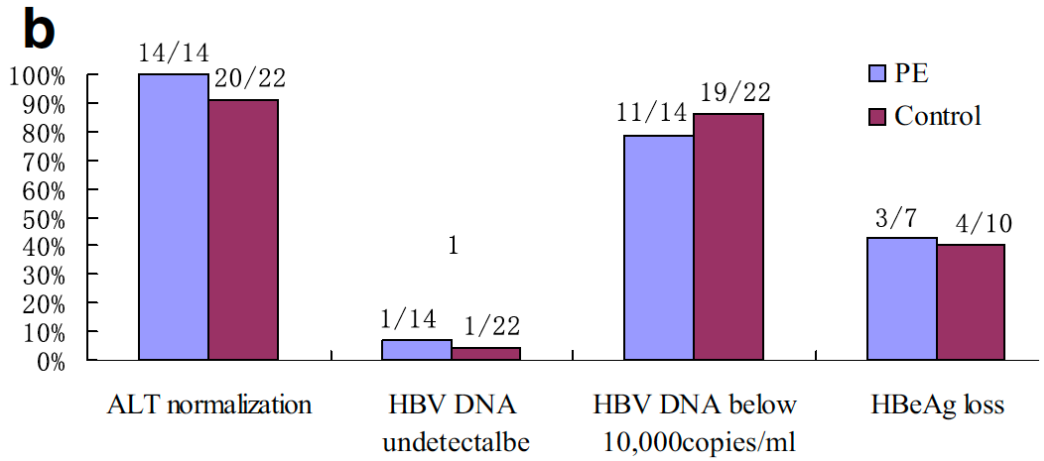
LL Xiao et al. Biomed Res Int 2019

Therapeutic Plasma Exchange for HBV-ACLF Patients

Retrospective study of 158 consecutive patients with HBV-ACLF (single center)
38 patients received 2–5 sessions of PE therapy



Survival	158	119	36	31	29
PE	38	38	14	13	12
Control	120	81	22	18	17

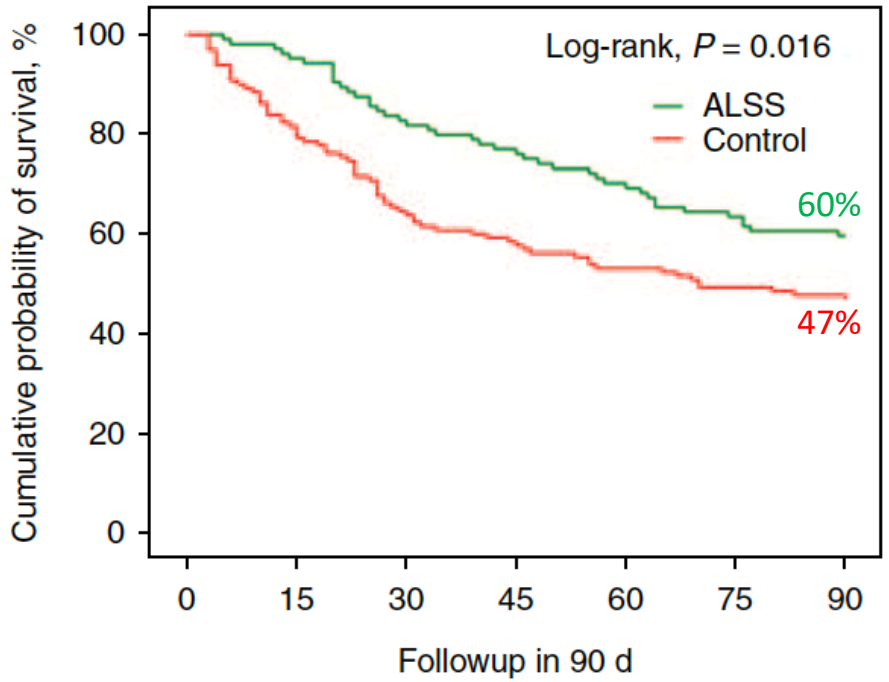


	HR	95 % CI	*p* value
Hepatic encephalopathy (yes/no)	6.03	3.241–10.768	<0.001
Ascites (yes/no)	2.712	1.419–4.638	0.002
Therapy without PE (yes/no)	1.983	1.295–3.036	0.001
MELD score	1.079	1.057–1.108	<0.001

YM Wan et al. Hepatol Int 2016

Randomized Trial of Plasma Exchange ALSS vs. SMT for HBV-related ACLF

- From January 2003 to December 2007, a total of 234 patients with HBV-associated ACLF not eligible for LT were enrolled
  - Plasma exchange-centered ALSS + SMT (ALSS group, n=104)
    - 3 routine treatments were performed in the first 10 days (once per 3–4 days)
  - SMT alone (control group, n=130)



- Median survival was 879 days in the ALSS group (43% survival at 5 years) and 649 days in the control group (31% survival at 5 years, P<0.05)
- ALSS was found to be associated with favorable outcome by both univariate and multivariate analysis.

	HR Value	95% CI	
Multivariate Analysis			
Sodium (per meq/dL increase)	0.94	0.90–0.99	0.02
Cirrhosis	1.24	0.92–1.69	0.04
HE (per grade increase)	1.49	1.05–2.11	0.03
HRS	2.89	1.81–4.60	<0.01
MELD score (per point increase)	1.09	1.02–1.16	<0.01
ALSS treatment	0.74	0.50–0.99	0.04

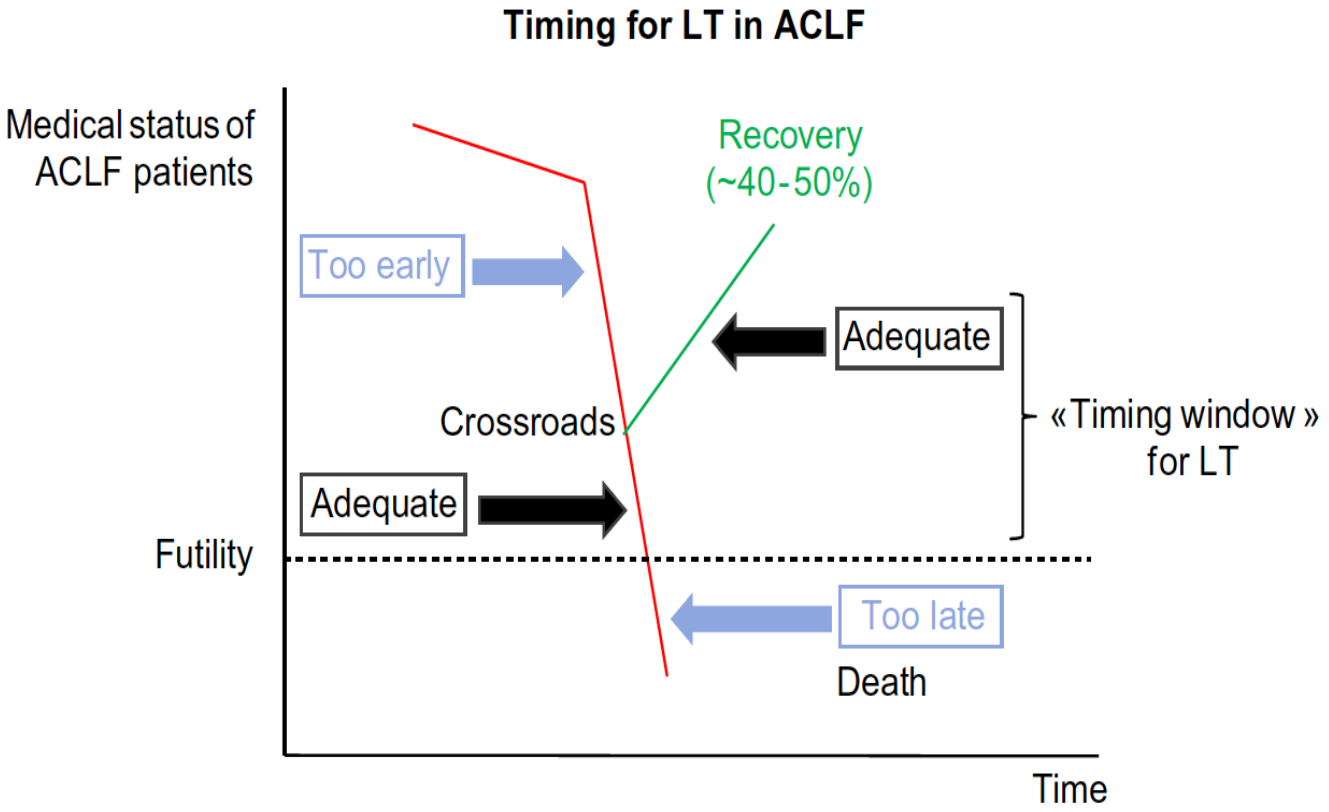
For 90-day mortality

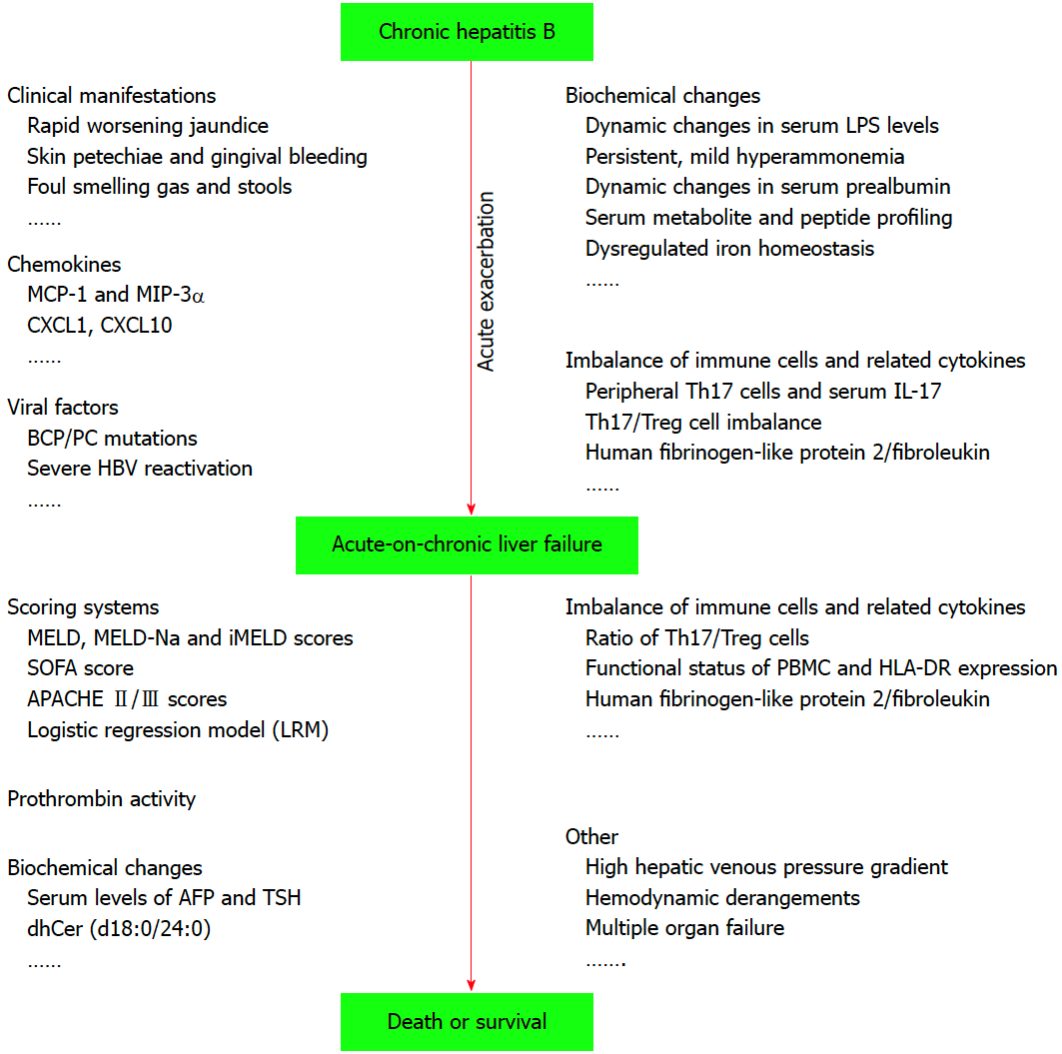
G Qin et al. Medicine 2014

Liver Transplantation and ACLF

- Definitive treatment for non-reversible ACLF
- All patients should be considered for evaluation if no contraindications
- High frequency of contraindications
  - “Too sick to transplant”
- Outcome data is scarce and difficult to interpret due to different ACLF definitions
- Timing of transplantation is crucial – short window of opportunity

Predictors of Outcomes in HBV-related ACLF and Timing of Liver Transplantation

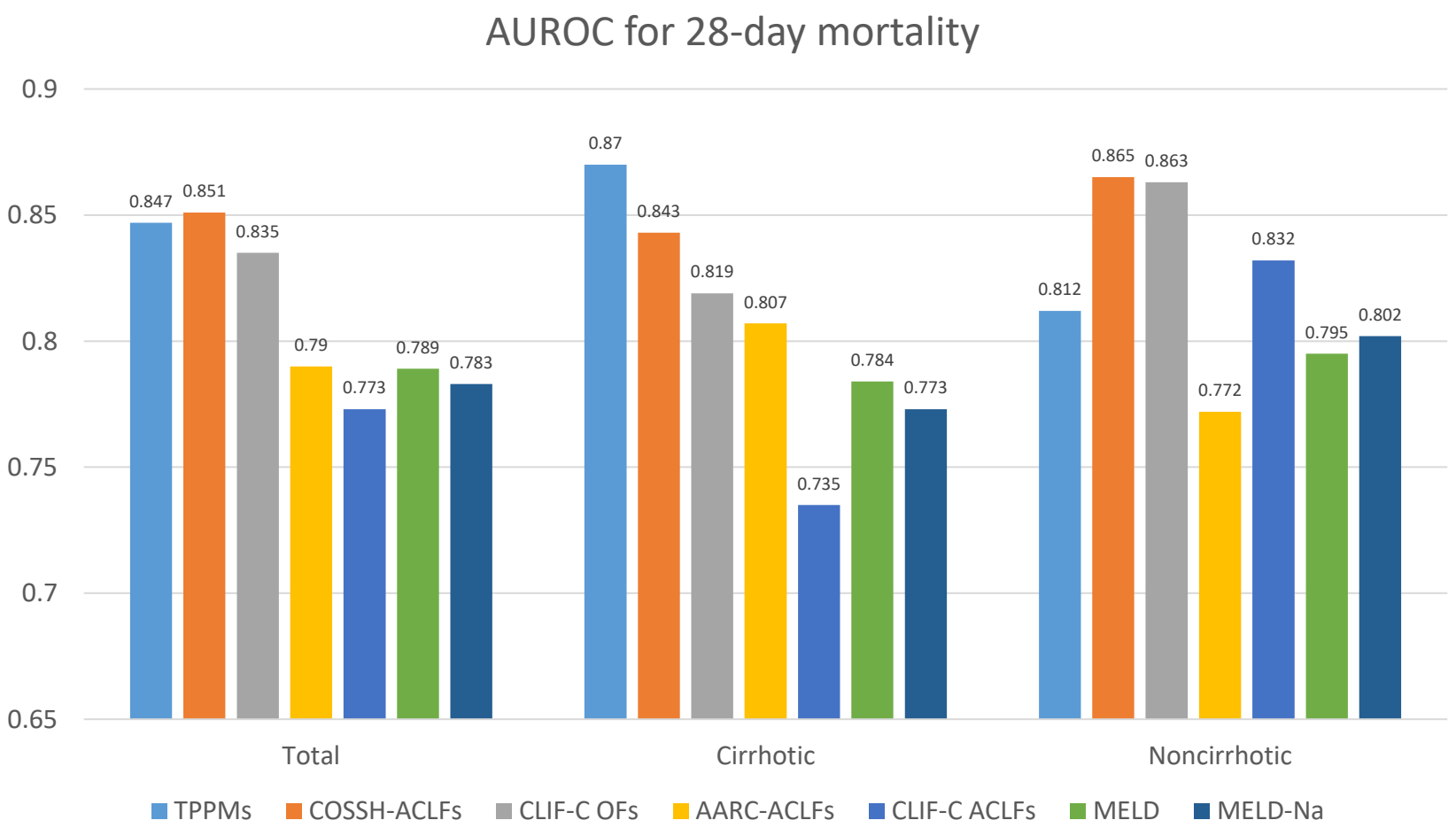




Gustot T & Moreau R. J Hepatology 2018

EQ Chen et al. World J Gastroenterol 2015

Comparison of Different Models in Predicting Short Term Mortality in HBV-ACLF



Tongji prognostic predictor model score (TPPMs)

$$\text{TPPM score } P = 1/\left(1 + e^{-\text{logit}(P)}\right)$$

$$\begin{aligned}\text{logit}(P) = {} & 0.003 \times [\text{total bilirubin } (\mu\text{mol/l})] \\ & + 0.951 \times \text{INR} + 2.258 \\ & \times [\text{constant for complications:} \\ & 0 \text{ if without or with 1 complication;} \\ & 1 \text{ with 2 ormore complications}] + 0.114 \\ & \times [\lg \text{HBV DNA(copies/mL)}] - 5.012.\end{aligned}$$

Chinese Group on the Study of Severe Hepatitis B-ACLF score
COSSH-ACLFs = 0.741*INR+0.523*HBV-SOFA+ 0.026*age+0.003*TB level

AARC score					
Points	Total bilirubin (mg/dl)	HE grade	PT-INR	Lactate (mmol/l)	Creatinine (mg/dl)
1	<15	0	<1.8	<1.5	<0.7
2	15–25	I–II	1.8–2.5	1.5–2.5	0.7–1.5
3	>25	III–IV	>2.50	>2.5	>1.5
Minimum 5, maximum 15					

AARC ACLF grade	
Grade	Score
I	5–7
II	8–10
III	11–15

T Chen et al. Hepatol Int 2019

Model of End-stage Liver Disease (MELD) Score to Predict Short Term Outcome in Severe HBV Flares

Parameter	Value
Total number	240
Age (years)	52 (21-81)
Male sex	192 (80.0%)
Alcohol use (≥20 g/day)	12 (5.0%)
Laboratory	
Bilirubin (μmol/L)	193 (51-719)
ALT (U/L)	1989 (502-11,443)
Albumin (g/L)	34 (16-46)
Creatinine (μmol/L)	73 (36-848)
INR	2 .1 (1.5-8.0)
Platelets ($\times 10^9$/L)	125 (12-327)
MELD score	24 (15-42)
Viral	
HBeAg positivity	49 (20.4%)
HBV DNA (log IU/mL)	7.77 (4.11-10.06)

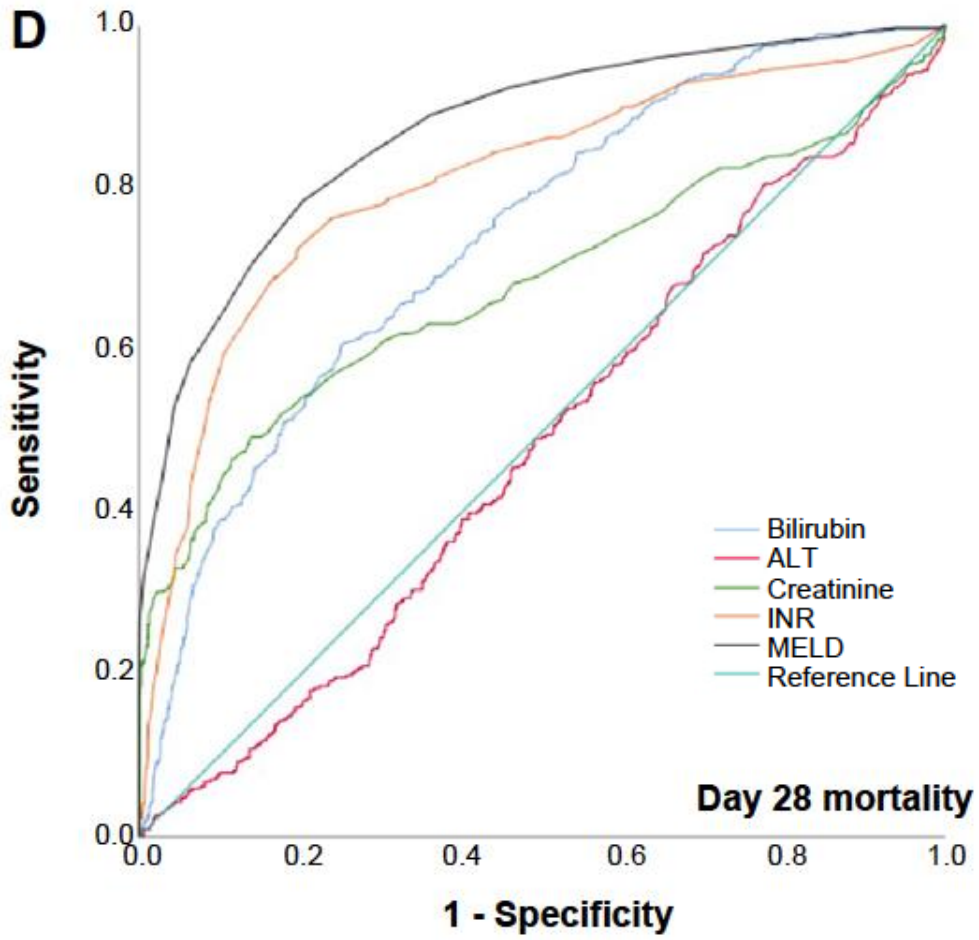
Inclusion criteria
- Age 18 years or older
- Evidence of acute flare of CHB
  - CHB infection
    - Known/documented history of infection and/or
    - Hepatitis B surface antigen positivity ≥ 6 months
  - ALT ≥ 10× upper limit of normal
  - HBV DNA ≥ 4 logs IU/mL
- Evidence of liver decompensation
  - Bilirubin ≥ 50 mmol/L
  - INR ≥ 1.5

Exclusion criteria
- Hepatitis from other causes
  - Acute hepatitis A
  - Acute hepatitis E
  - Drug-induced liver injury

- Laboratory data was collected at time of admission until date of discharge or death/liver transplantation
- A total of 4,021 timepoints were collected, and randomized to training (n=2019) & validation sets (n=2002)
- MELD score was calculated for each of these 4,021 timepoints, and day 7, 14, 21, and 28 mortality determined
- For patients who underwent LT, the pooled data was used only if they were still alive at those specific time points, and censored thereafter.

J Fung et al. Hepatology 2020

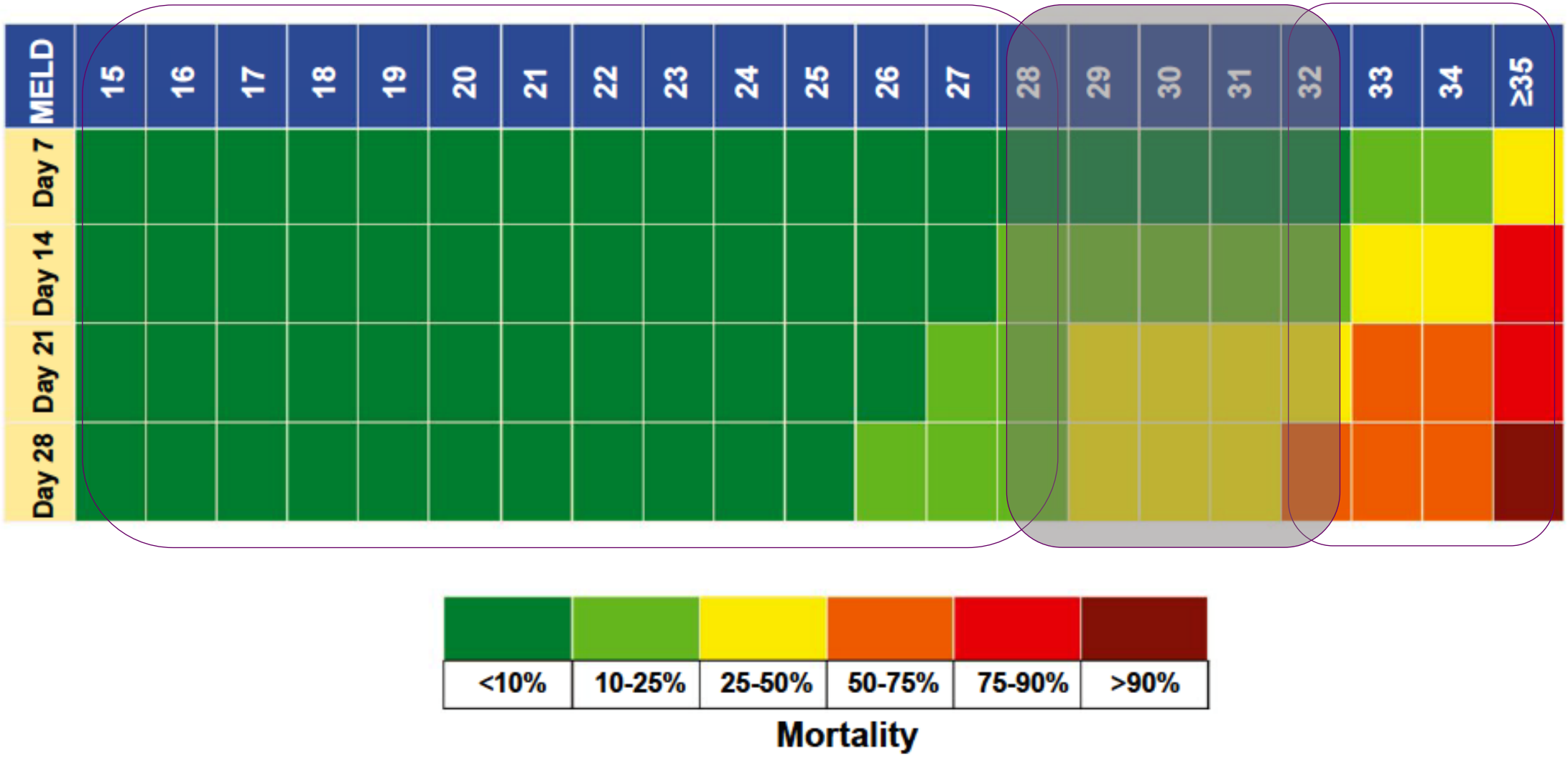
AUROC of Pooled MELD Score in Predicting Day 7, 14, 21, and 28 Mortality



Mortality	Day 7	Day 14	Day 21	Day 28
Optimal MELD cutoff	32	29	28	28
Training set				
AUROC	0.909	0.892	0.883	0.871
Sensitivity	78.8%	80.9%	82.6%	77.2%
Specificity	87.0%	79.9%	77.1%	79.7%
Positive predictive value	36.2%	47.1%	53.1%	61.1%
Negative predictive value	97.8%	95.0%	93.4%	90.1%
Validation set				
AUROC	0.913	0.893	0.877	0.875
Sensitivity	77.1%	81.0%	81.5%	78.3%
Specificity	88.4%	79.2%	78.5%	82.6%
Positive predictive value	36.1%	44.8%	54.7%	66.1%
Negative predictive value	97.9%	95.2%	93.0%	89.8%

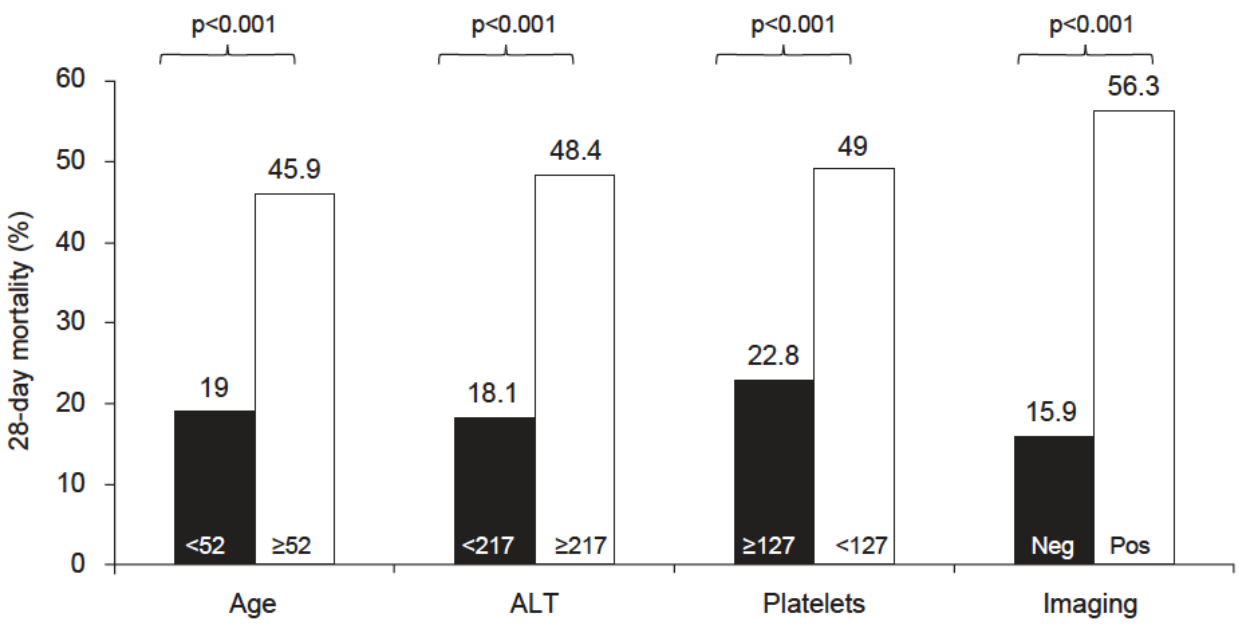
J Fung et al. Hepatology 2020

MELD-Based Predictor of Short-Term Mortality in Severe Flares of Chronic Hepatitis B

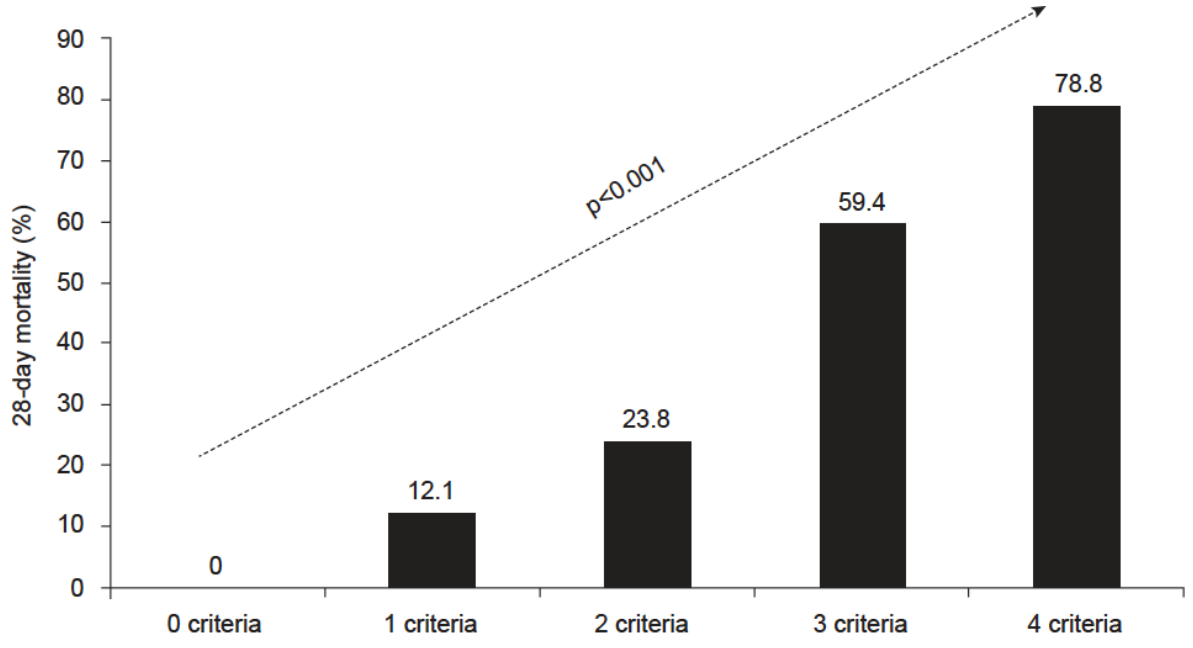


Additional Criteria for MELD 28-32
Age, ALT, Platelets, Imaging

28-day mortality stratified by age, ALT level, platelet levels, and imaging findings for MELD 28-32

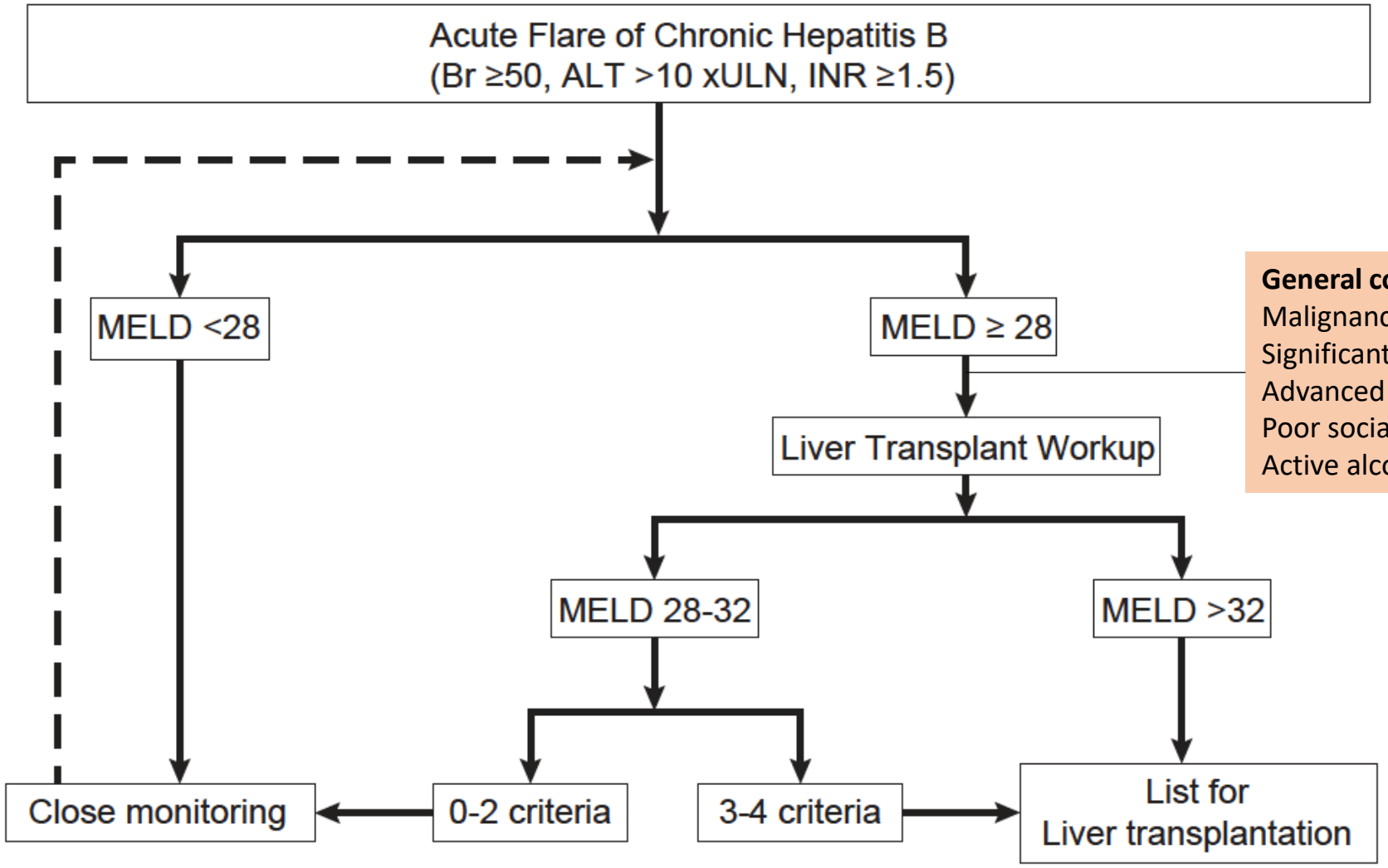


28-day mortality according to number of at-risk criteria for MELD 28-32



Imaging = abnormal US/CT at baseline as defined by cirrhosis (coarse nodular/shrunken liver), and/or ascites, and/or splenomegaly

Proposed Algorithm to Evaluate Patients with HBV-related ACLF



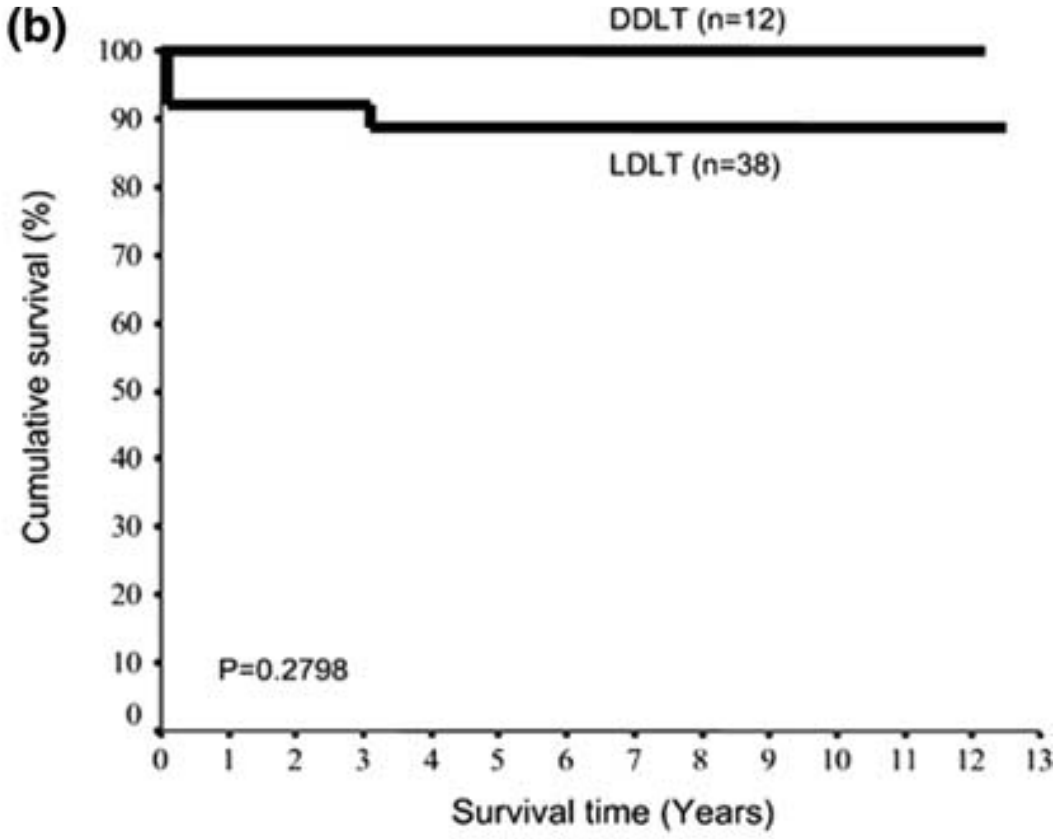
General contra-indication for LT
Malignancy
Significant medical co-morbidity
Advanced age
Poor social support
Active alcoholism

Contra-indications for LT
Uncontrolled sepsis
Refractory shock
Uncontrolled bleeding
ARDS

J Fung et al. Hepatology 2020

DDLT vs LDLT for HBV-related ACLF

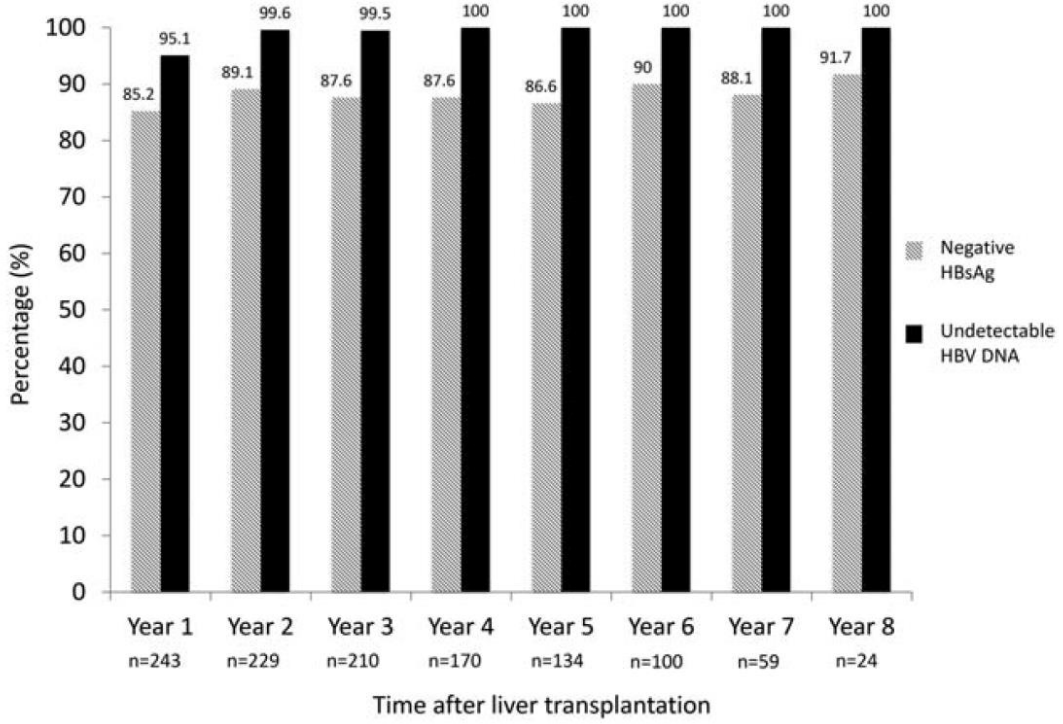
- In regions where LT is available, donor organs remains scarce, and a significant number may not receive timely DDLT
- LDLT is an important therapeutic option where graft supply is limited
  - No survival difference between DDLT vs. LDLT for HBV-related ACLF
- 5-year overall survival rate of patients with acute-on-chronic liver failure exceeded 90%

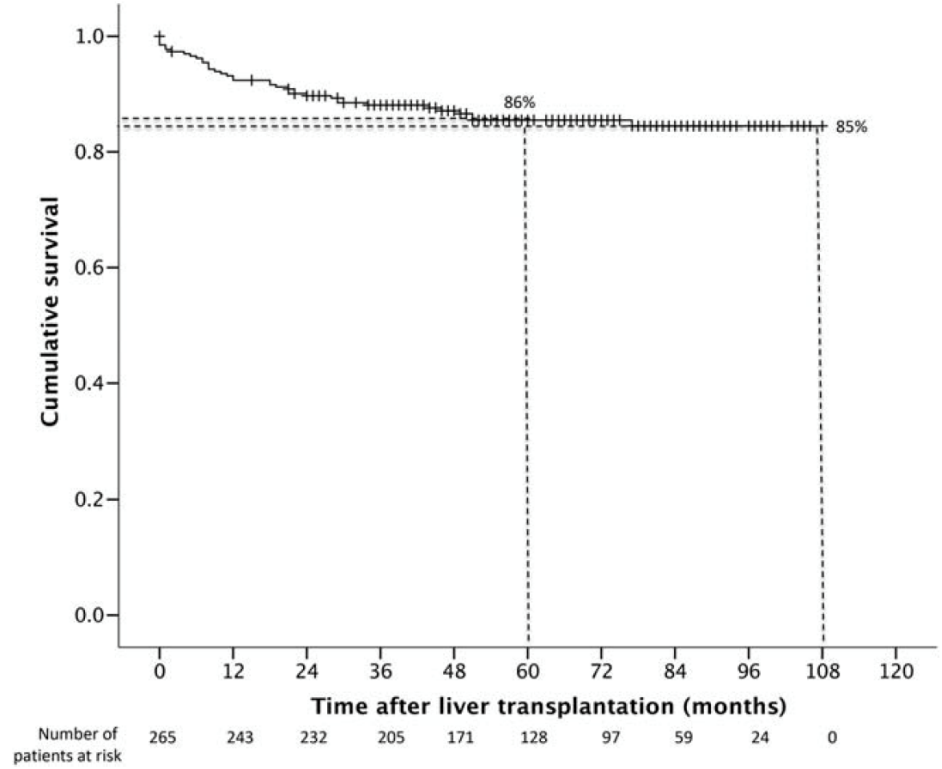


Chan AC et al, Hepatol Int 2009

Post-Transplant Survival for CHB

- Antiviral prophylaxis is required long-term to prevent HBV reactivation after LT
  - Excellent long-term survival with as completely HBIG-free regimen using NUCs alone





J Fung et al. Hepatology 2017

Summary (I)

- Despite the availability of NUCs for over two decades, severe acute flares of CHB remains the leading cause of ACLF in Asia
- Early commencement of NUCs with high potency and high barrier to resistance with dose adjusted for renal function
- Nutritional assessment and support is essential to ensure adequate caloric intake and to reduce malnutrition
- Early identification of complications and appropriate preventive strategies
  - Infections, GI bleeding, AKI, hepatic encephalopathy

Summary (II)

- Early referral to a liver transplant center is important for severe acute flares with evidence of ACLF
- MELD score remains an important prognostic indicator for determining short term outcome, and the need for liver transplantation
- Excellent long term survival can be achieved with liver transplantation for HBV, with long term NUCs prophylaxis required to prevent reactivation

Summary (III)

- There is still much to learn!
  - Glucocorticoid use
  - G-CSF
  - ALSS

  - Which patient will benefit the most / harmful
  - Timing of therapy
  - Optimal treatment regimen

Thank You Very Much For Your Attention

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