10TH ANNUAL

DIGESTIVE DISEASES: NEW ADVANCES

September 29–30, 2023

Hyatt Regency Jersey City On The Hudson

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Liver Transplant Evaluation: When to Start?

Nancy Reau, MD

Relevant Disclosures

Nancy Reau, MD

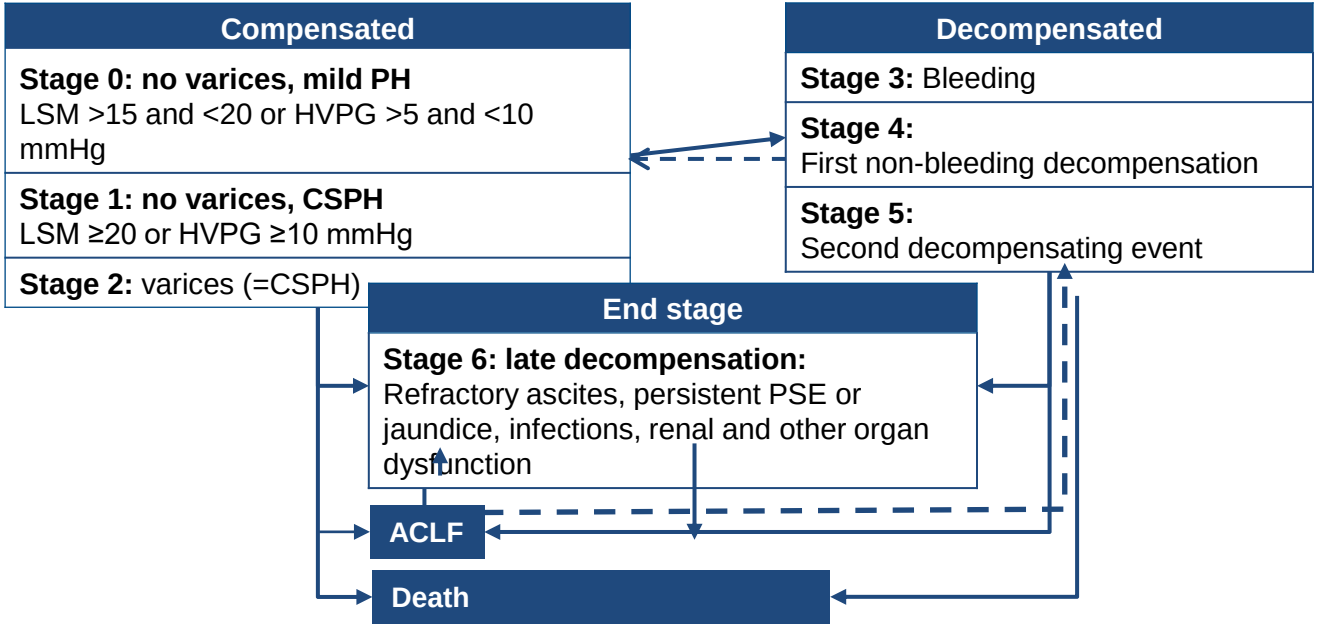
- **Research Support:** Gilead, AbbVie
- **Consultant**: Salix, Intercept

Agenda – Review

- Liver transplant in end stage liver disease (ESLD)
- Acute Liver Failure (ALF)
- Transplant for other stuff

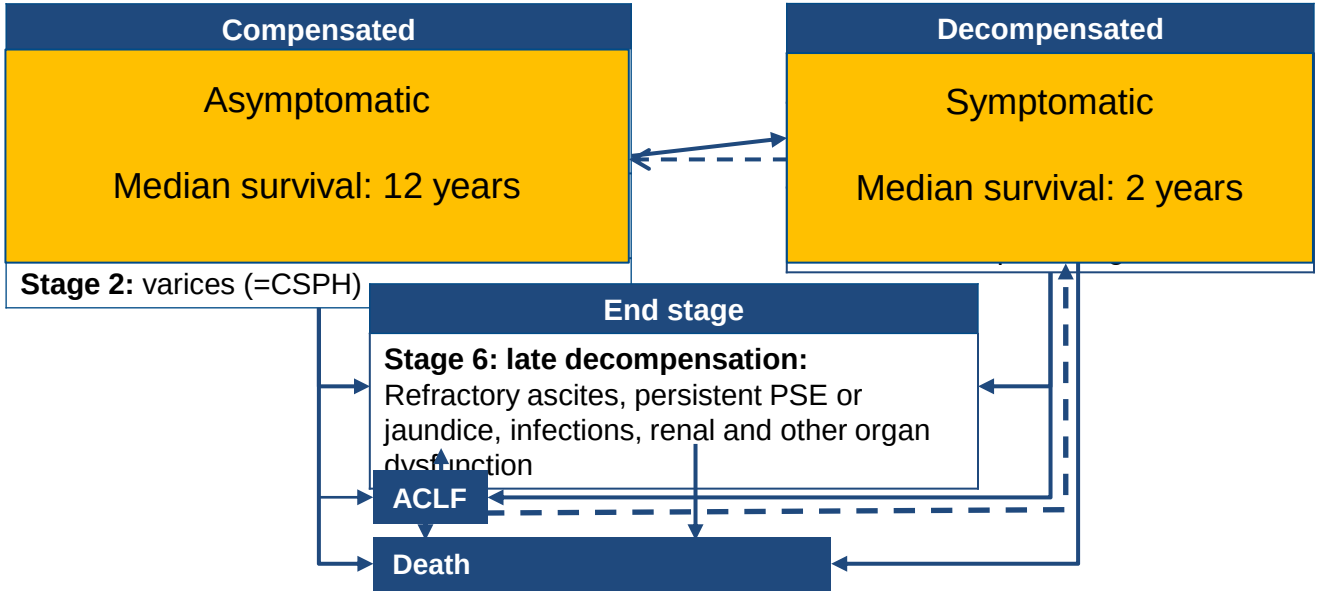
Multi-Stage Model for the Clinical Course of Cirrhosis

- Transition from compensated cirrhosis to DC occurs at a rate of ~5–7% per year
- DC is a systemic disease, with multi-organ/system dysfunction



D'Amico G et al. *J Hepatol.* 2018;68:563–76; EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024.

Multi-Stage Model for the Clinical Course of Cirrhosis



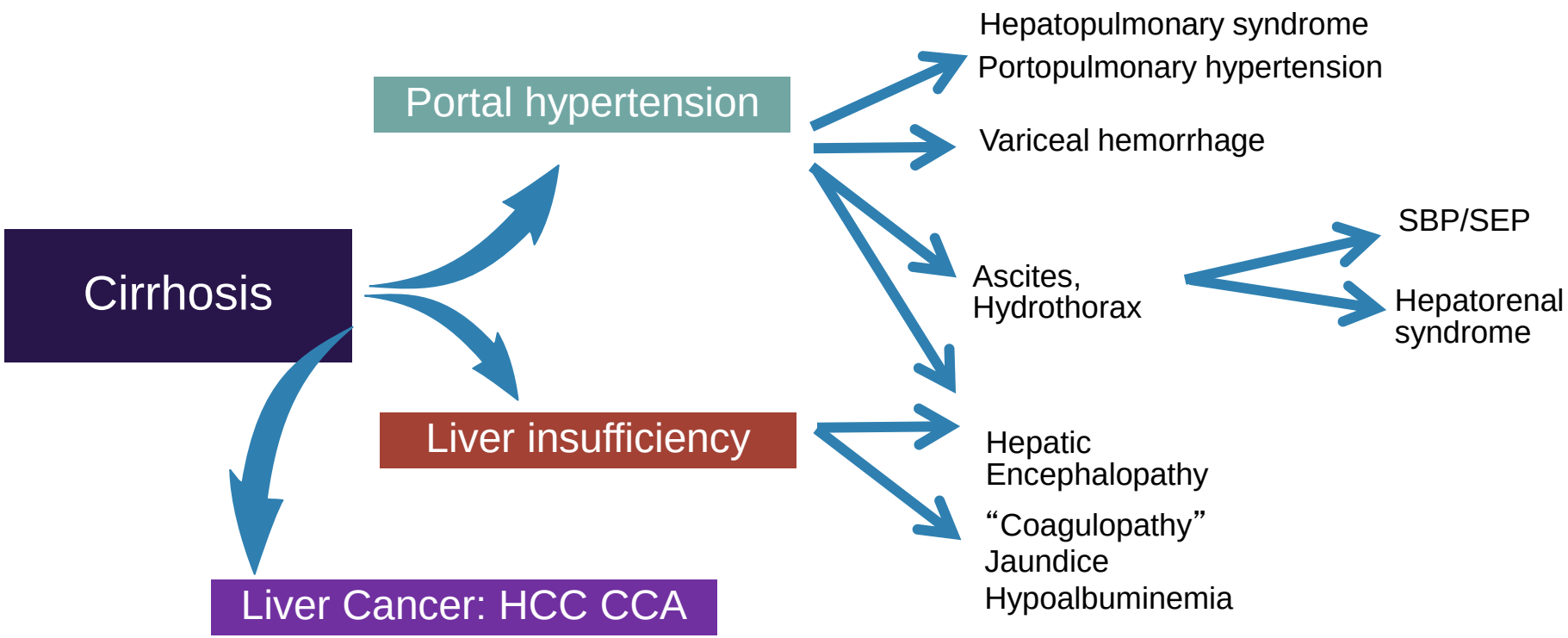
D'Amico G et al. *J Hepatol.* 2018;68:563–76; EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024.

Overall Management of DC

- Management should aim to **prevent progression**
  - Eliminate the etiology for the liver disease
  - Prevent malnutrition and sarcopenia
- No treatment exists that can act on cirrhosis progression directly
- Early recognition for those at risk and referral to transplant

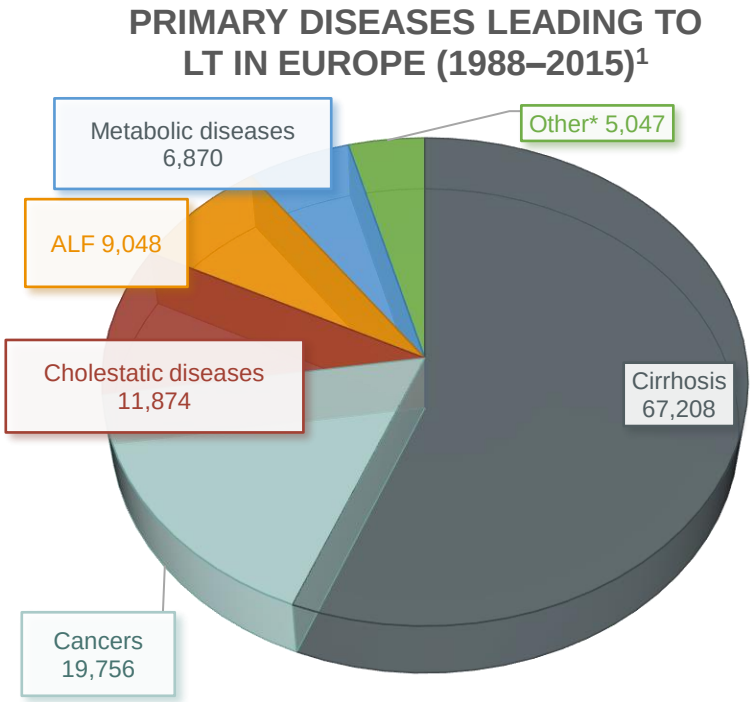
EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024.

Complications of Cirrhosis



The Candidate for LT: Indications

- **LT should be considered**:
  - LT would extend life beyond that predicted by the natural history of underlying liver disease
  - LT is likely to improve QoL
- **Patients should be selected** if:
  - Expected survival without LT is ≤1 year
- **Standard indications**:
  - ESLD
  - HCC
  - ALF



*Benign liver tumours or polycystic diseases, 1,658; Budd–Chiari, 1,020; parasitic diseases, 91; hepatopulmonary syndrome, 18; other liver diseases, 2,260.

1. ELTR. Available at: http://www.eltr.org/Overall-indication-and-results.html. Accessed 23.02.18; EASL CPG LT. *J Hepatol.* 2016;64:433–85.

The Candidate for LT: Score and Prognostic Factors for ESLD

- Timing is crucial
  - Before life-threatening complications occur
  - Not so early that benefits are outweighed by the risk of surgery and immunosuppression for life
- Priority for LT determined by MELD
  - MELD score ≥15 is recommended to list patients with ESLD
  - Only MELD >35 predicts post-LT mortality
- MELD does not reflect the impact of all complications
  - **MELD exceptions**
  - Extra points given to prioritize for LT

Exceptions to MELD score
Manifestations of cirrhosis • Refractory ascites • Recurrent gastrointestinal bleeding • Recurrent encephalopathy or chronic encephalopathy • Hepatopulmonary syndrome • Portopulmonary hypertension • Intractable pruritus
Miscellaneous liver diseases • Budd–Chiari syndrome • Familial amyloidotic polyneuropathy • Cystic fibrosis • Hereditary haemorrhagic telangiectasia • Polycystic liver disease • Primary oxaluria • Recurrent cholangitis • Uncommon metabolic disease
Malignancy • CCA, HCC • Uncommon liver tumours

EASL CPG LT. *J Hepatol.* 2016;64:433–85.

9.5 Specific Standardized MELD or PELD Score Exceptions

Candidates are eligible for MELD or PELD score exceptions or extensions that do not require evaluation by the NLRB if they meet *any* of the following requirements for a specific diagnosis of *any* of the following:

- Cholangiocarcinoma (CCA), according to *Policy 9.5.A: Requirements for Cholangiocarcinoma MELD or PELD Score Exceptions*
- Cystic fibrosis, according to *Policy 9.5.B: Requirements for Cystic Fibrosis MELD or PELD Score Exceptions*
- Familial amyloid polyneuropathy, according to *Policy 9.5.C: Requirements for Familial Amyloid Polyneuropathy (FAP) MELD or PELD Score Exceptions*
- Hepatic artery thrombosis, according to *Policy 9.5.D: Requirements for Hepatic Artery Thrombosis (HAT) MELD Score Exceptions*
- Hepatopulmonary syndrome, according to *Policy 9.5.E: Requirements for Hepatopulmonary Syndrome (HPS) MELD or PELD Score Exceptions*
- Metabolic disease, according to *Policy 9.5.F: Requirements for Metabolic Disease MELD or PELD Score Exceptions*
- Portopulmonary hypertension, according to *Policy 9.5.G: Requirements for Portopulmonary Hypertension MELD or PELD Score Exceptions*
- Primary hyperoxaluria, according to *Policy 9.5.H: Requirements for Primary Hyperoxaluria MELD or PELD Score Exceptions*
- Hepatocellular carcinoma, according to *Policy 9.5.I: Requirements for Hepatocellular Carcinoma (HCC) MELD or PELD Score Exception*

https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf.

CPT Score and MELD

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	**Points***		
	1	2	3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged *or*	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3
*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)			
Class A = 5 to 6 points			
Class B = 7 to 9 points			
Class C = 10 to 15 points			

To determine your MELD score, please complete the form below.

This calculator is recommended for ages 12 and older.
All fields are required.

Date of Birth(mm/dd/yyyy)

Bilirubin(mg/dl) **Serum Sodium**(mEq/L) **INR**

Serum Creatinine(mg/dl)

Had dialysis twice, or 24 hours of CVVHD, within a week prior to the serum creatinine test?

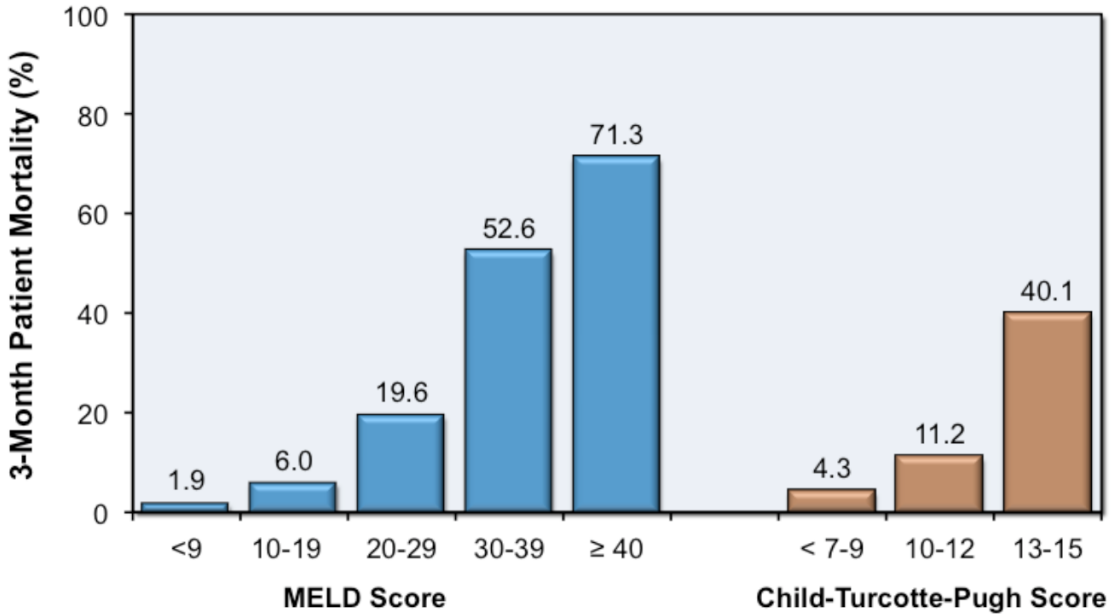
Yes No

Note: Creatinine will default to 4 mg/dl with a positive response.

Reset Calculate

http://hepatitisc.uw.edu/go/management-cirrhosis-related-complications/liver-transplantation-referral/core-concept/all.

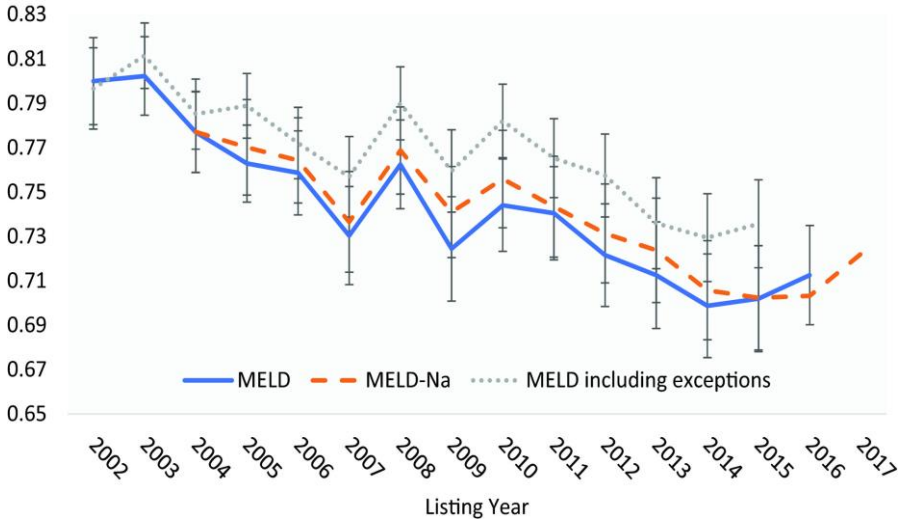
3 Month Mortality

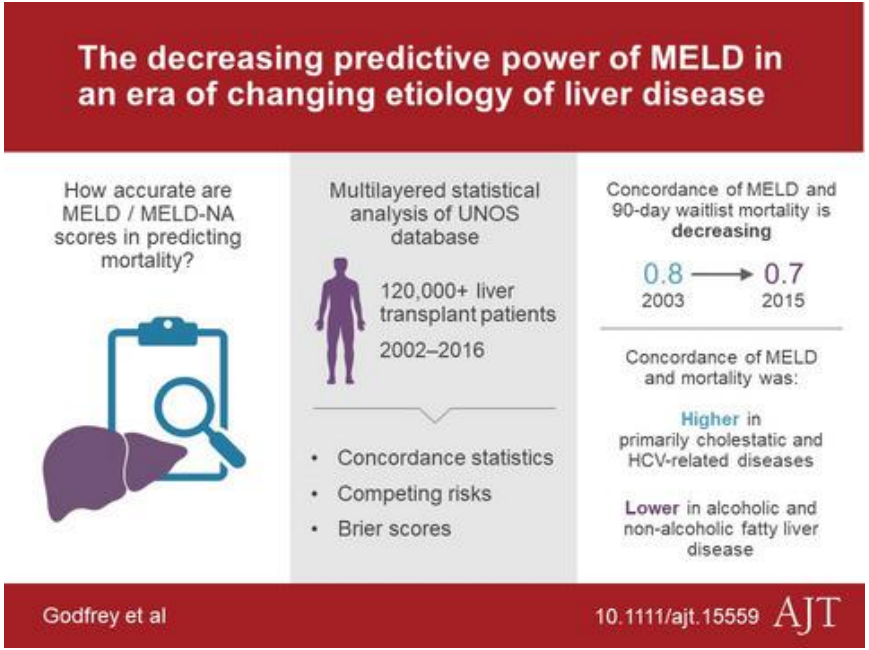


Recommend referral to a liver transplant center MELD ≥ 10 or CTP score ≥ 7

Wiesner R. *Gastroenterology*. 2003;124:91-6.

The Decreasing Predictive Power of MELD in an Era of Changing Etiology of Liver Disease





American J Transplantation. Volume: 19, Issue: 12, Pages: 3299-3307, First published: 08 August 2019, DOI: (10.1111/ajt.15559).

MELD: The journey as yet!

Predict survival following TIPSS
Short period, common metric of disease severity

Initially etiology imp in TIPS
Alc, Cholestatic >>Viral

Ascites, VB, HE, SBP – not improve MELD
Quantitative tests X

MELD in LTx
- Decr WL registration (12%)
- Decr WL mortality (15%)

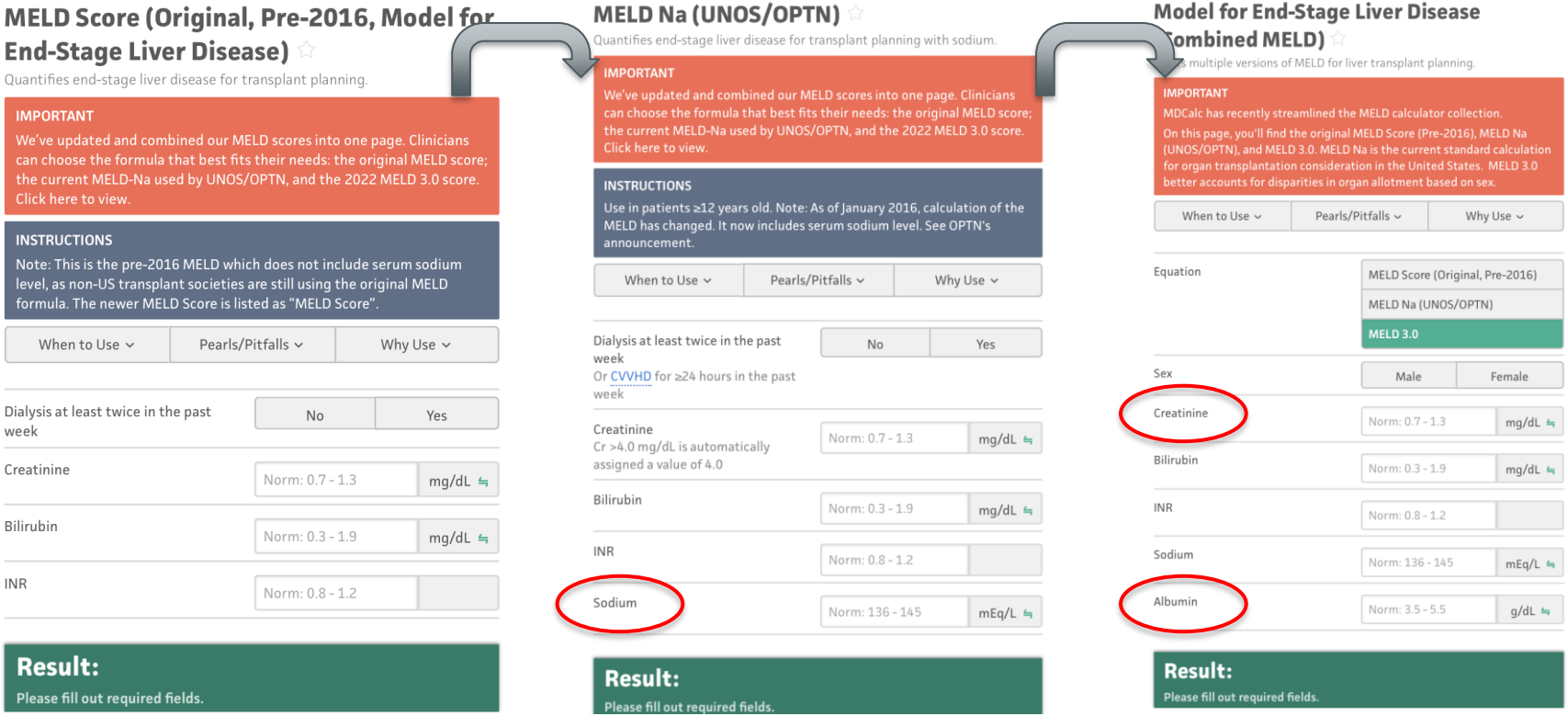
MELD Na+ from 2016

MELD not predictive of Post LT outcome
Less useful in LDLT
Modification by UNOS empirical!!

- Serum Creatinine - lot of weightage!! (esp CKD, Bil >25)
- Women are disadvantaged - S Cr overestimating renal function and underestimating risk of mortality.
- Na+ fluctuates- diuretic, free water

Source: Twitter!

MELD Score – An Evolving Story



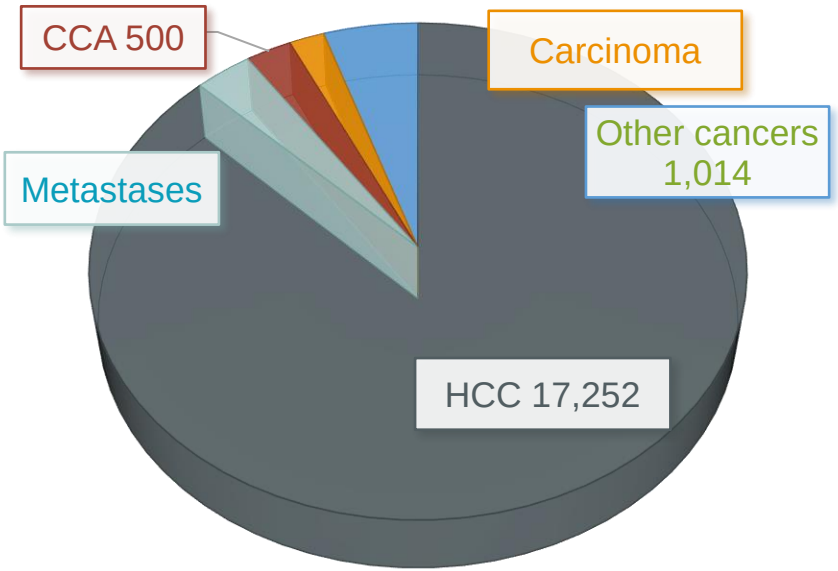
When to Start?

- Decompensated ESLD → MELD >10
- When to list… More info needed
  - MELD >15
  - Blood Type
  - Exception points
  - Center outcomes
    - Death on the wait list
    - Time to transplant
    - 1 and 3 year outcomes
- Final decision should be made within each expert center by a multidisciplinary group of staff
  - Considering risks and benefits for individual patients

Management of Patients With Liver Cirrhosis and Hepatic Malignancies

- LT is indicated:
  - HCC
  - CCA
  - Other malignancies (w/o Mets)
  - Hepatic metastases
- The dropout rate from LT waiting lists is ~15–30% due to HCC progression
  - Downstaging and bridging treatment should be offered to all patients expected to wait >6 months
- CCA accounts for 5–20% of primary liver tumours
  - LT for CCA remains controversial due to a high risk of recurrence

Hepatobiliary cancers as primary disease for LT in Europe (1988–2015)[1]



1. ELTR. Available at: http://www.eltr.org/Specific-results-by-disease.html. Accessed 23.02.18; EASL CPG LT. *J Hepatol.* 2016;64:433–85.

Liver Transplantation in HCC

- HCC is the most common primary tumour of the liver
- LT is suitable for early, unresectable HCC
- 5-year survival exceeds 70% when Milan criteria are used
- Expanded criteria have shown similar outcomes

Milan criteria remain the benchmark

Milan criteria
Solitary HCC <5 cm diameter **OR** ≤3 nodules with diameter <3 cm
UCSF criteria[1]
Single lesion ≤6.5 cm in diameter **OR** 2–3 lesions ≤4.5 cm; total tumour diameter ≤8 cm

AFP model[2]	Points*
Largest diameter, cm	
≤3	0
3–6	1
>6	4
Nodules, n	
1–3	0
≥4	2
AFP level, ng/ml	
≤100	0
100–1,000	2
>1,000	3

*Total score ≤2 associated with low risk of recurrence and 5-year survival ~70%

1. Yao FY et al. *Hepatology.* 2001;33:1394–403; 2. Duvoux C et al. *Gastroenterology.* 2012;143:986–94; EASL CPG LT. *J Hepatol.* 2016;64:433–85.

Clinical Gastroenterology and Hepatology
Volume 21, Issue 6, June 2023, Pages 1475-1484

UNOS Down-staging Criteria for Liver Transplantation of Hepatocellular Carcinoma: Systematic Review and Meta-Analysis of 25 Studies

1 Study Selection

Participants: Adult patients with HCC, that are deemed sutiable to undergo downstaging treatment.

Intervention: Patients with HCC who had undergone down-staging treatment by locoregional therapies, such as TACE or TARE, or a combination of therapies, for tumors initially beyond MC

Outcomes: Proportion of patients that were successfully down-staged to within MC, dropped out of the LT waitlist, underwent LT, HCC recurrence and overall survival .

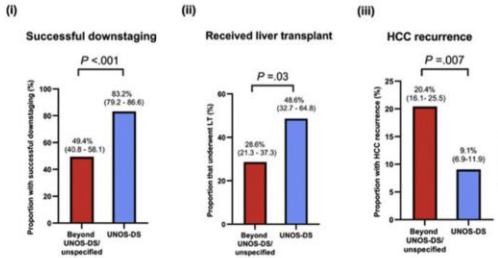
2 Findings

We screened 1,059 articles and included 25 articles involving 3,997 patients.

Patients from studies using UNOS-DS criteria had lower MELD score, lower AFP at listing, lower cumulative tumor diameter, and fewer HCC nodules compared to studies beyond UNOS-DS/ no specified tumor burden.

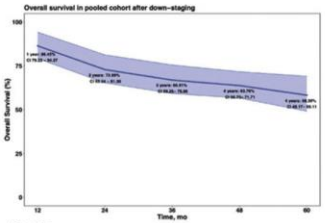
Overall, 51.82% underwent successful down-staging, 32.83% underwent LT and 16.08% developed HCC recurrence.

Summary of key outcomes of downstaging, by criteria used for baseline tumor burden

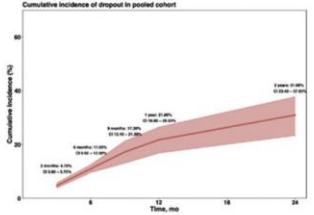


Overall pooled survival after Downstaging/LT

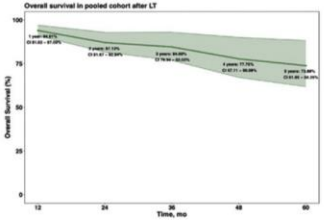
Intention-to-treat



Incidence of dropout



After LT



3 Conclusion

Only half of all HCC patients underwent down-staging successfully and a third received LT.

Among studies that utilized the UNOS-DS criteria, downstaging was successful in four-fifths, half received LT and post-LT outcomes were excellent.

For patients within the UNOS-DS criteria, the intention-to-treat 1- and 5- year survival for was 86% and 58% respectively. 1- and 5- year post-LT survival was 94% and 74% respectively.

Keywords: LT, Liver Transplant; HCC, Hepatatocellular Carcinoma; UNOS-DS, United Network of Organ Sharing Down-staging; TACE, trans-arterial chemoembolization; TARE, trans-arterial radioembolization; MC, Milan Criteria

Clinical Gastroenterology and Hepatology

Liver Transplantation

- Demand for organs far outstrips the supply,
- The etiologies of cirrhosis are shifting: Increased alcohol-associated liver disease and metabolic fatty liver disease and less viral hepatitis
- Attention to how patients are selected for transplantation and the strategies needed to prevent recurrent disease

Comorbidities

- All LT candidates require evaluation for comorbidities
  - CV, respiratory, renal
  - Infections
  - Nutrition
  - Anatomy
  - Neoplastic lesions
  - Social assessment, psychiatric and addiction

- There is no formal age limit
  - Patients >65 years of age need a multidisciplinary evaluation

- LT has been performed successfully in patients >70 years
  - Increased risk of CV complications

EASL CPG LT. *J Hepatol.* 2016;64:433–85.

Evaluation Should Be Efficient

Published in final edited form as:
Transplantation. 2022 January 01; 106(1): 72–84. doi:10.1097/TP.0000000000003615.

Evaluation Within Thirty Days of Referral for Liver Transplantation is Associated with Reduced Mortality: A Multi-Center Analysis of Patients Referred Within the VA Health System

Binu V John, MD[1], Kaley Schwartz, BS[1], Andrew R Scheinberg, MD[2], Bassam Dahman, PhD[3], Seth Spector, MD[4,5], Yangyang Deng, MS[3], David Goldberg, MD[6], Paul Martin, MD[6], Tamar H. Taddei, MD[7,8], David E. Kaplan, MD[9,10]

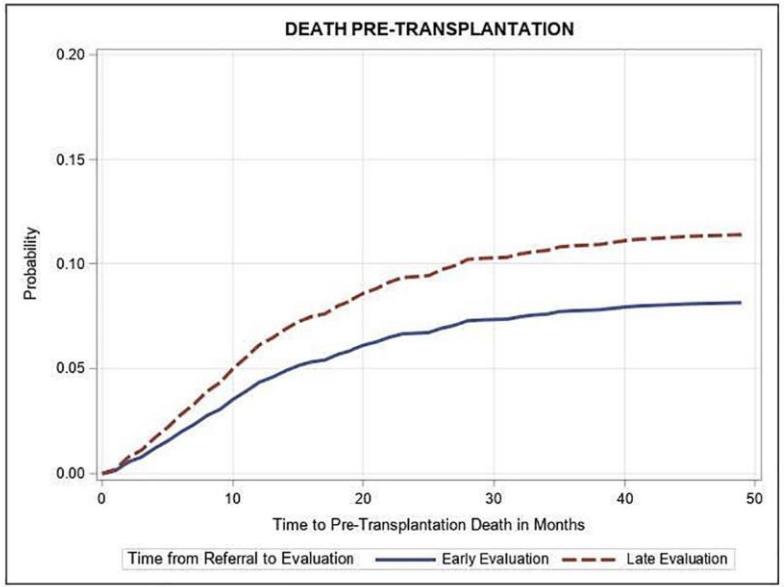


Figure 2:
Figure 2: Adjusted time from referral to pre-transplant death, by early (≤30 days) versus late (>30 days) time from referral to evaluation

What About Acute on Chronic Liver Disease?

Acute Decompensation (AD)

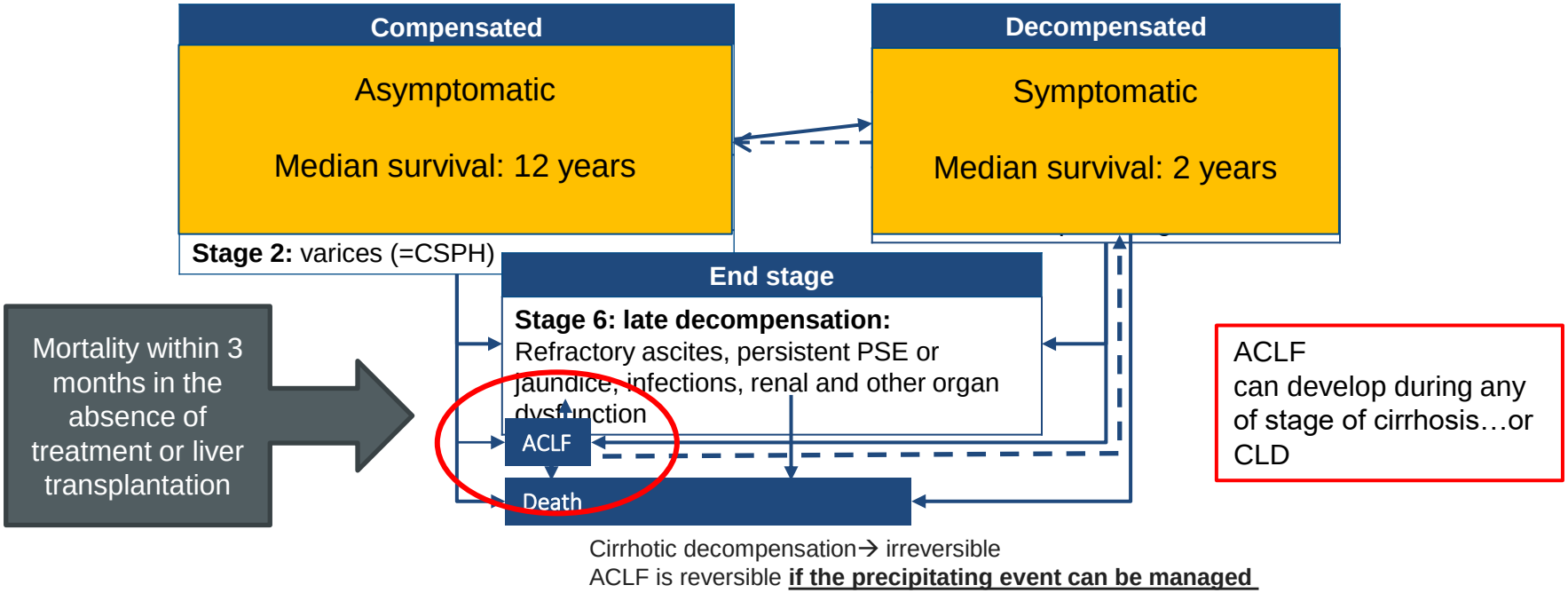
- Cirrhosis with recent development of complications of liver disease
  - Ascites
  - Variceal hemorrhage
  - Hepatic Encephalopathy (HE)
  - Spontaneous bacterial infections
    - SBP (peritonitis)
    - SBE (infected hydrothorax)
    - SB (bacteremia)

Acute Decompensation (AD) **+High 28d Mortality**

- Cirrhosis with recent development of complications of liver disease
  - Ascites
  - Variceal hemorrhage
  - Hepatic Encephalopathy (HE)
  - Spontaneous bacterial infections
    - SBP (peritonitis)
    - SBE (infected hydrothorax)
    - SB (bacteremia)
- AD with intense systemic inflammatory response
- Close association with precipitating factors
  - Infections
  - rHBV
  - Alcoholic hepatitis
  - DILI
- Single or multiple organ failures

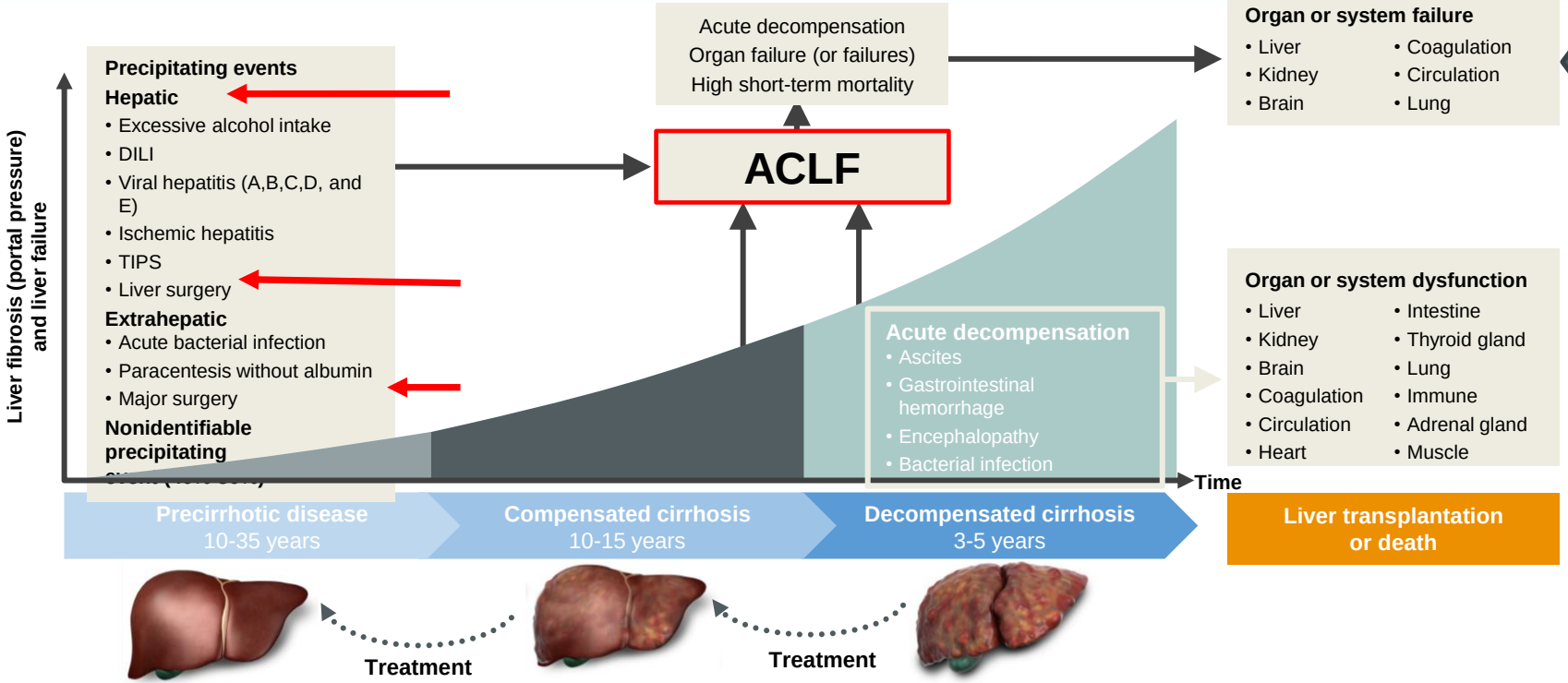
Multi-Stage Model for the Clinical Course of Cirrhosis

- Transition from compensated cirrhosis to DC occurs at a rate of ~5–7% per year
- DC is a systemic disease, with multi-organ/system dysfunction



D'Amico G et al. *J Hepatol.* 2018;68:563–76; EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024.

Natural Course of Liver Disease

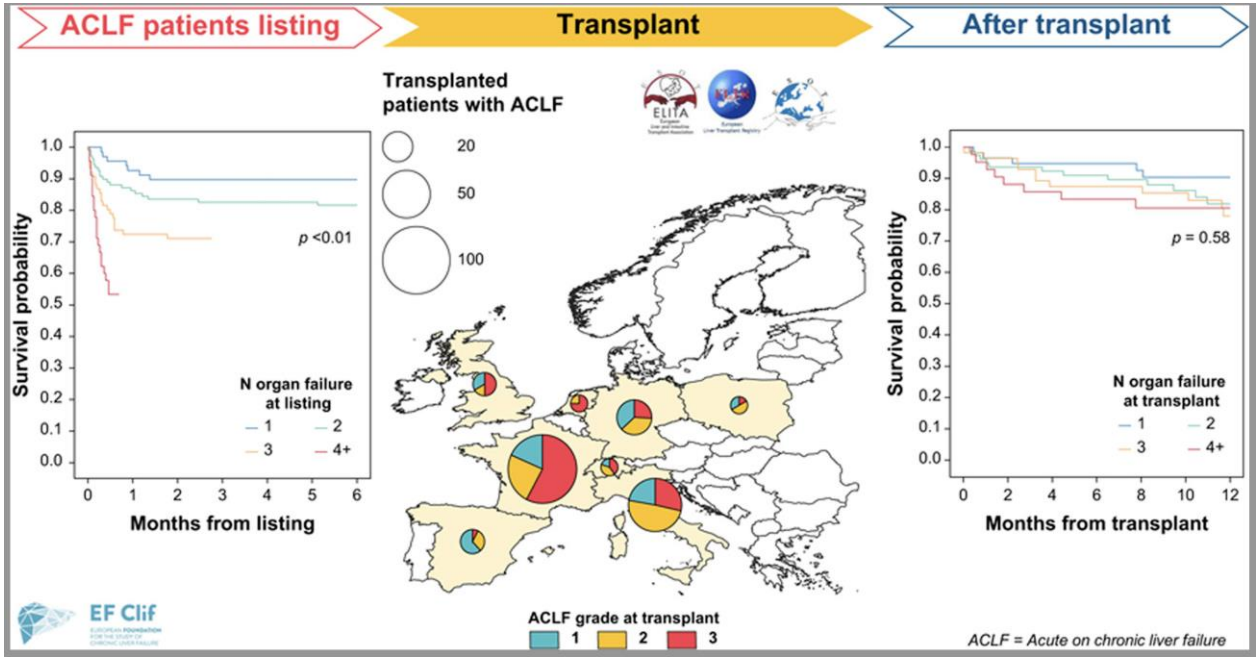


DILI, drug-induced liver injury ; TIPS, transjugular intrahepatic portosystemic shunt.
Arroyo V et al. *Nat Rev Dis Primers*. 2016;2:16041.

Recognizing ACLF: Alphabet Soup of Definitions

Organ	APASL ACLF Research Consortium	EASL CLIF-C ACLF	NACSELD
Liver	Total Bilirubin PT/INR	Total bilirubin PT/INR	--
Kidney	Creatinine	Creatinine/Dialysis	Dialysis
Brain	HE grade	HE grade	HE grade III/IV
Circulatory	Lactate	MAP, vasopressors	MAP, vasopressors
Respiratory	--	PaO_2 or SpO_2 / FiO_2	Mechanical ventilation
Major Organ failure Category	**Predominantly Hepatic failure variables**	**Combination of hepatic and extrahepatic organ failure variables**	**Predominantly extrahepatic organ failure variables**

Liver Transplantation for Patients With Acute-on-Chronic Liver Failure (ACLF) in Europe: Results of the ELITA/EF-CLIF Collaborative Study (ECLIS)☆



Increased Post-LT mortality:

- Pre-LT arterial lactate levels >4 mmol/L
- Recent infection from MDR organisms
- Renal replacement therapy

1-year survival on the LT waiting list: 73% for ACLF-1 or -2 and 50% for ACLF-3.

Liver Transplantation for Patients With Acute-on-Chronic Liver Failure (ACLF) in Europe: Results of the ELITA/EF-CLIF Collaborative Study (ECLIS)☆

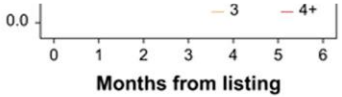
ACLF patients listing | Transplant | After transplant

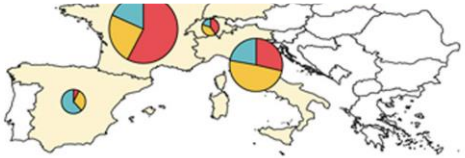
Review

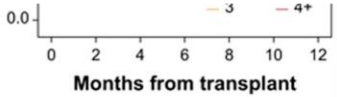
Journal of Hepatology, June 2023. vol. 78 j 1118–1123

Should patients with acute-on-chronic liver failure grade 3 receive higher priority for liver transplantation?

Florent Artru[1,†], David Goldberg[2,†], Patrick S. Kamath[3,*]







EF Clif

ACLF = Acute on chronic liver failure

Increased Post-LT mortality:

JOURNAL OF HEPATOLOGY

MDR

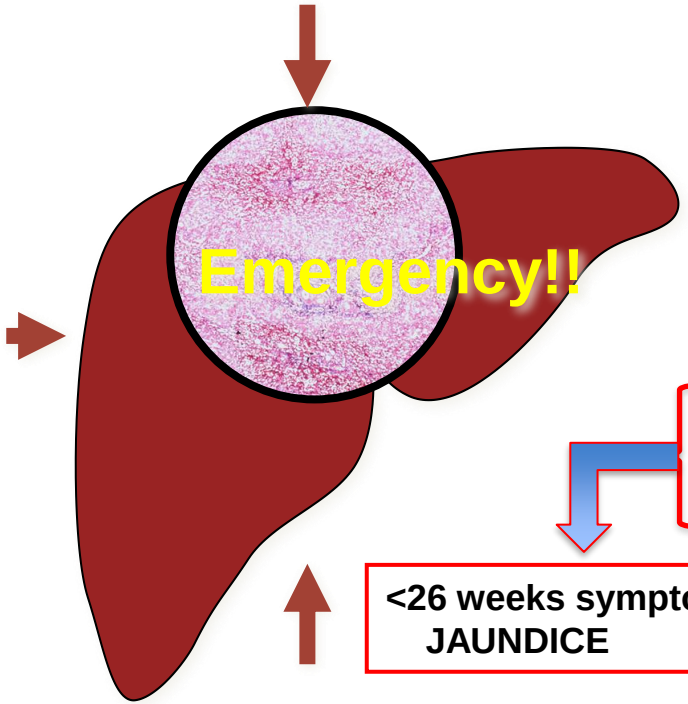
erapy

waiting list: 73% for ACLF-1 or -2 and 50% for ACLF-3.

Acute Liver Failure (ALF)

- **Acute Liver Failure:** acute abnormality of liver blood tests in an individual without underlying chronic liver disease.
  - Associated with development of a coagulopathy of liver etiology, as opposed to the coagulation disturbance seen in sepsis, and clinically apparent altered level of consciousness due to HE.
- **Acute liver injury:** patients who develop coagulopathy, but do not have any alteration to their level of consciousness

Acute Liver Failure: Early Recognition (Fulminant Hepatic Failure or Fulminant Hepatitis)



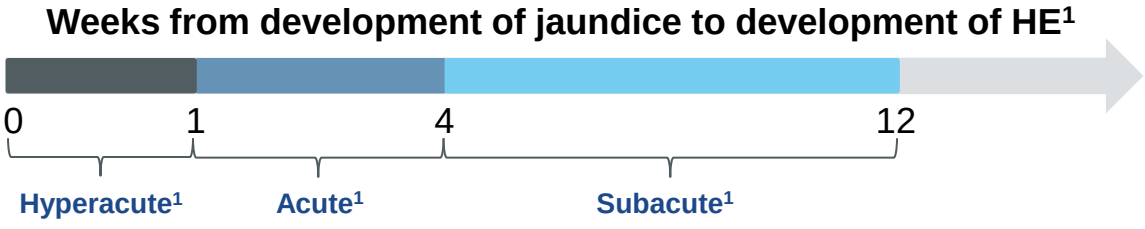
Diagnosis:

- **Severe acute liver injury**
- **INR ≥1.5**
- **Hepatic encephalopathy**

<26 weeks symptoms
JAUNDICE

- **No underlying liver disease**

Sub-Classifications of ALF

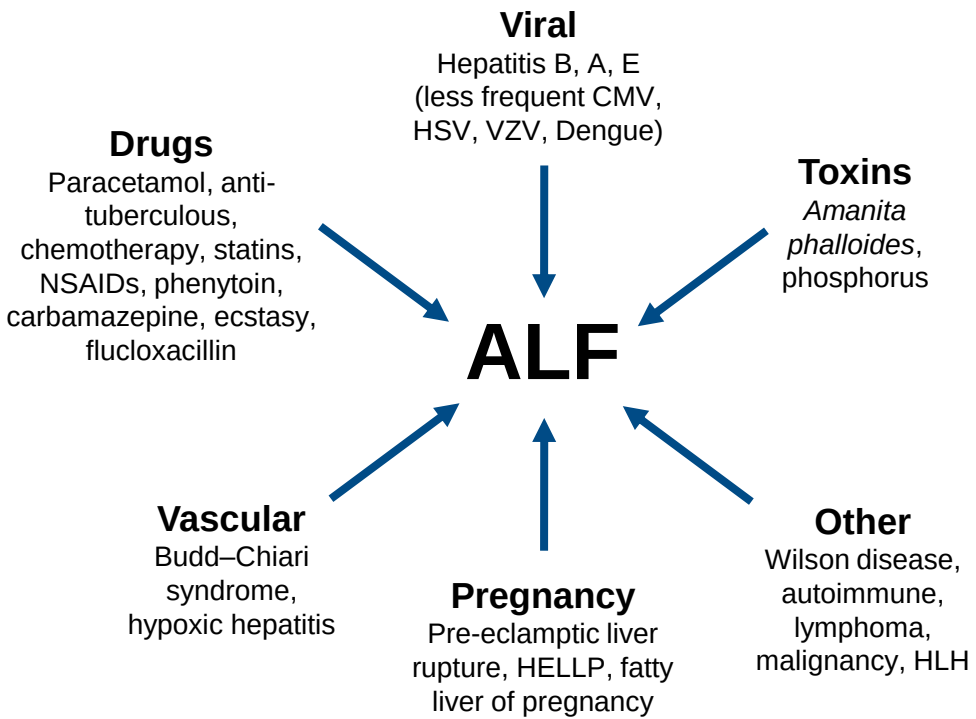


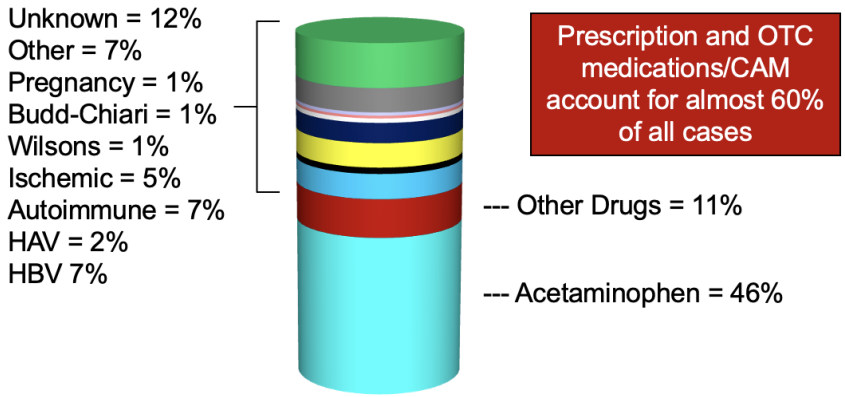
Hyperacute[1]	Acute[1]	Subacute[1]	
+++	++	+	Severity of coagulopathy[2]
+	++	+++	Severity of jaundice[2]
++	++	+/-	Degree of intracranial hypertension[2]
Good	Moderate	Poor	Chance of spontaneous recovery[2]
Paracetamol HAV, HEV	HBV	Non-paracetamol drug-induced	Typical cause[2]

+++ High severity; ++ Medium severity; + Low severity; +/- Present or absent

1. O'Grady JG et al. *Lancet.* 1993;342:273–5; 2. Bernal W, et al. Lancet 2010;376:190–201; EASL CPG ALF. *J Hepatol.* 2017;66:1047–81.

Principal Etiologies of ALF





EASL CPG ALF. *J Hepatol.* 2017;66:1047–81; WM Lee. *Clin Liver Dis*. 2013; 17:575-586.

Assessment and Management at Presentation

- **Immediate measures**
  - Assess suitability for liver transplant and initiate early discussions with transplant unit
    - Even if not immediately relevant

Suggested criteria for referral of cases of ALF to specialist units

Paracetamol and hyperacute aetiologies	Non-paracetamol
Arterial pH <7.30 or HCO_3 <18	pH <7.30 or HCO_3 <18
INR >3.0 day 2 or >4.0 thereafter	INR >1.8
Oliguria and/or elevated creatinine	Oliguria/renal failure or Na <130 mmol/l
Altered level of consciousness	Encephalopathy, hypoglycaemia or metabolic acidosis
Hypoglycaemia	Bilirubin >300 µmol/l (17.6 mg/dl)
Elevated lactate unresponsive to fluid resuscitation	Shrinking liver size

EASL CPG ALF. *J Hepatol.* 2017;66:1047–81.

Criteria for Emergency Liver Transplantation

King's College criteria	
ALF due to paracetamol • Arterial pH <7.3 after resuscitation and >24 hours since ingestion • Lactate >3 mmol/L or • The 3 following criteria: – HE >Grade 3 – Serum creatinine >300 µmol/L – INR >6.5	**ALF not due to paracetamol** • INR >6.5 or • 3 out of 5 following criteria: – Aetiology: indeterminate aetiology, hepatitis, drug-induced hepatitis – Age <10 years or >40 years – Interval jaundice encephalopathy >7 days – Bilirubin >300 µmol/L – INR >3.5

Beaujon-Paul Brousse criteria (Clichy)
• Confusion or coma (HE stage 3 or 4) • Factor V <20% of normal if age <30 years or • Factor V <30% if age >30 years

80% mortality without OLT

EASL CPG ALF. *J Hepatol.* 2017;66:1047–81.

Status 1 (More than ALF)

- Fulminant liver failure
- Anhepatic
- Primary Non-Function of a transplant organ
- Non-Function of a transplanted segment
- HAT (Hepatic Artery Thrombosis)
- Acute decompensated Wilson Disease

https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf.

Differences Between ALF and ACLF

Table 6. Differences between ALF and ACLF

	ALF	ACLF
Age	Younger	Older
Chronic liver disease	Absent	Present Signs of portal hypertension
Precipitating factors (by frequency)	DILI, viral hepatitis, autoimmune hepatitis	Infection, alcohol, GI bleeding,
Clinical signs	Liver injury, INR>1.5, HE	Coagulopathy, elevated bilirubin, shock, multiorgan dysfunction
Liver biopsy	Necrosis and collapse	Fibrosis
CNS	Increased intracranial pressure Use CRRT early for HE	HE responds to lactulose/Rifaximin
Infection	Late (<5 d)	Early (<5 d)
Renal failure	Hypoperfusion, ATN	HRS-AKI
Respiratory	ARDS rare	ARDS common
Liver transplantation	KCC, MELD Status 1A listing	MELD No priority in MELD system

ACLF, acute on chronic liver failure; ALF, acute liver failure; ARDS, acute respiratory distress syndrome; ATN, acute tubular necrosis; CNS, central nervous system; CRRT, continuous renal replacement therapy; DILI, drug-induced liver injury; GI, gastrointestinal; HE, hepatic encephalopathy; HRS-AKI, hepatorenal syndrome-acute kidney injury; INR, international normalized ratio; KCC, King's College Criteria; MELD, Model for End-Stage Liver Disease.

Acute Liver Failure Guidelines. *Official journal of the American College of Gastroenterology* | ACG118(7):1128-1153, July 2023.

These Rules Change!

Questions???

OPTN | ORGAN PROCUREMENT AND TRANSPLANTATION NETWORK

Policies

https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf.