OneGI

SECOND ANNUAL GI & LIVER *Summit*

Complications of Cirrhosis and HCC Detection – Caring for the Cirrhotic Patient

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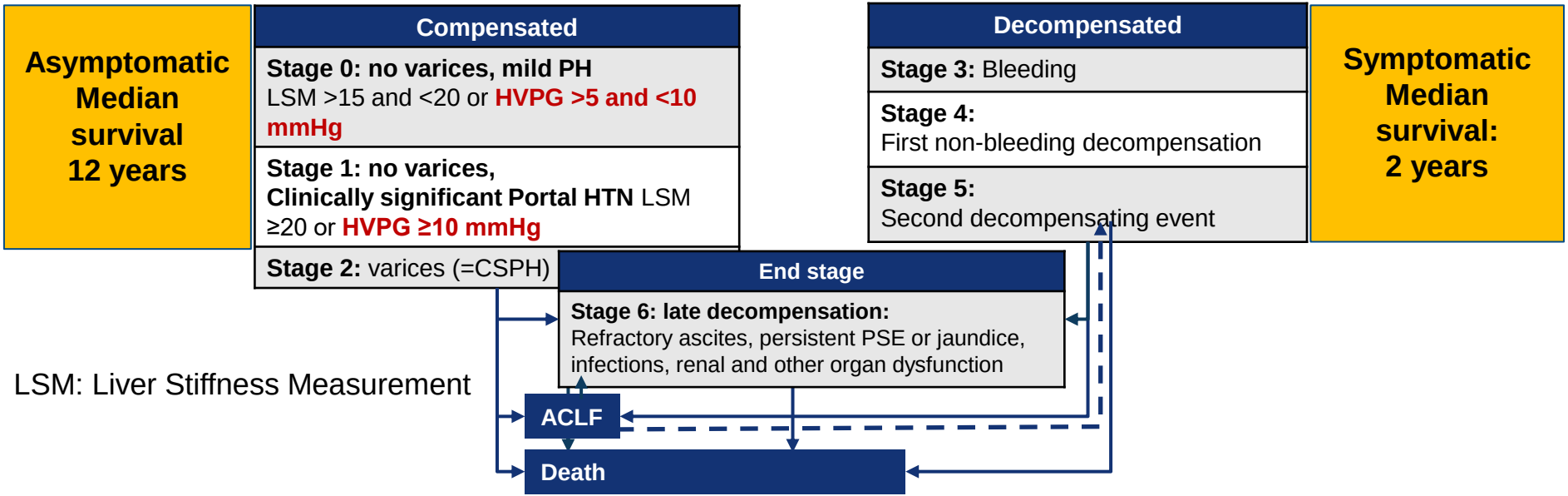
Multi-Stage Model for the Clinical Course of Cirrhosis

- 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



LSM: Liver Stiffness Measurement

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;
Ripoll C. Groszmann R. Garcia-Tsao G. *Gastroenterology.* 2007; **133**: 481-488.

Multi-Stage Model for the Clinical Course of Cirrhosis

Recompensate

Disease Modifying Strategies

Etiological RX
- HCV/ HBV
- Weight Loss (bariatric surgey GLP 1 agonists)
- Antisteatotic

Reduce Fibrosis
- Statins
- Antifibrotic drugs (upcoming)

Reduce Portal HTN: Delay Progression

- Beta Blockers
- Preemptive low diameter TIPS

Compensated	Decompensated
Stage 0: no varices, mild PH LSM >15 and <20 or HVPG >5 and <10	**Stage 3:** Bleeding
Stage 1: no varices, CSPH LSM ≥20 or HVPG ≥10 mmHg	**Stage 4:** First non-bleeding decompensation
Stage 2: varices (=CSPH)	**Stage 5:** Second decompensating event

Living Donor Liver Transplant

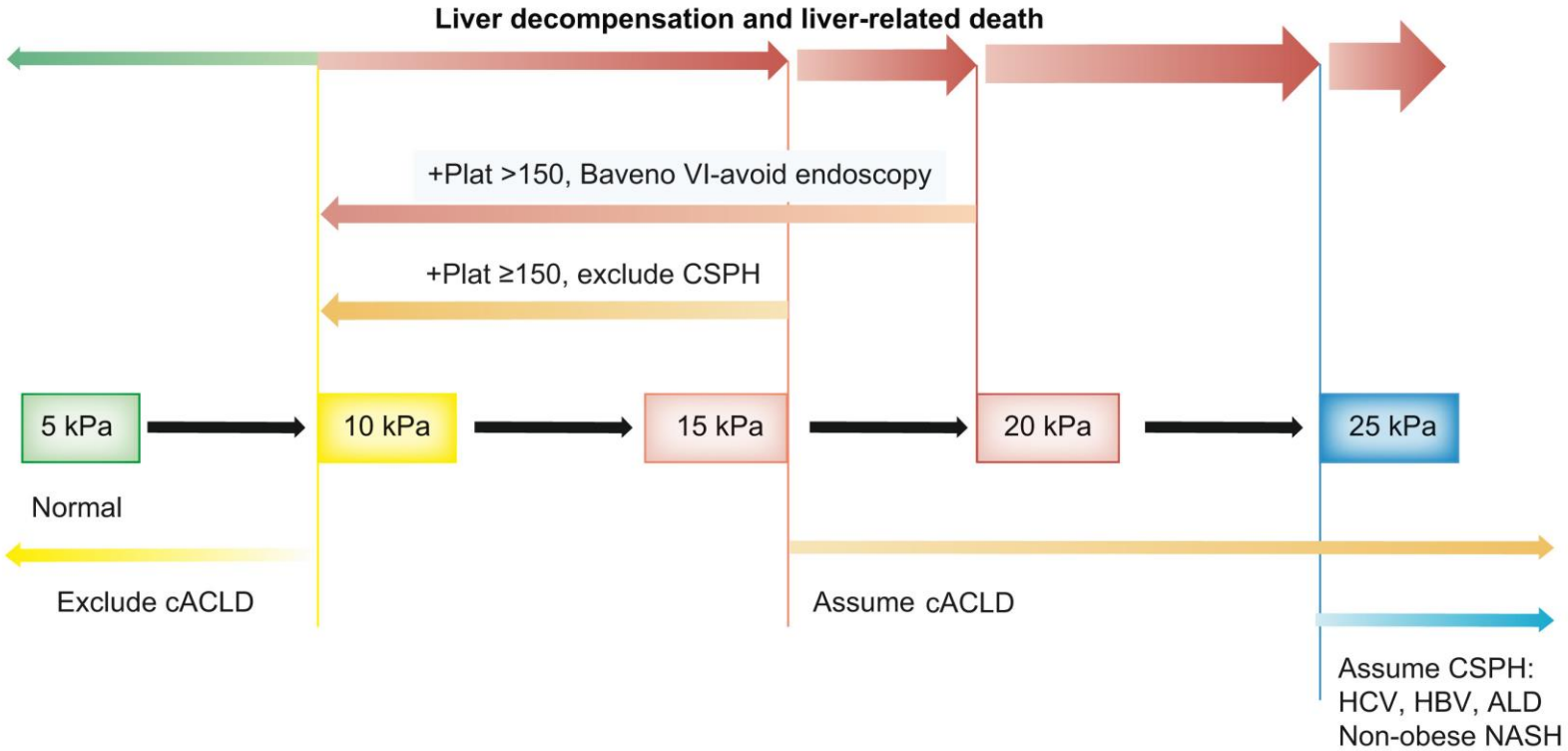
End stage
Stage 6: late decompensation: Refractory ascites, persistent PSE or jaundice, infections, renal and other organ dysfunction

Liver Transplant

ACLF

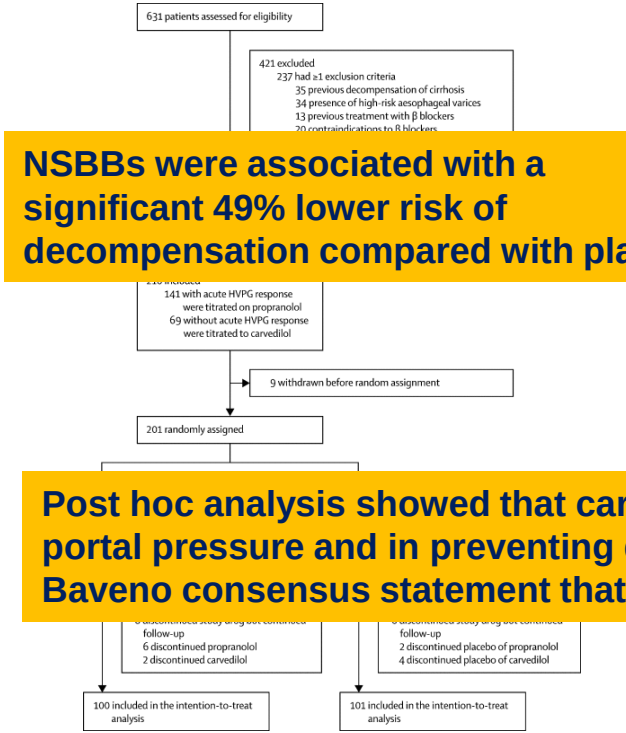
Ripoll C. Groszmann R. Garcia-Tsao G. *Gastroenterology.* 2007; 133: 481-488; D'Amico G et al. *J Hepatol.* 2018;68:563–76; EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024.

Non Invasive Assessment of Clinically Significant Portal HTN Liver Stiffness Measurement (Fibroscan)

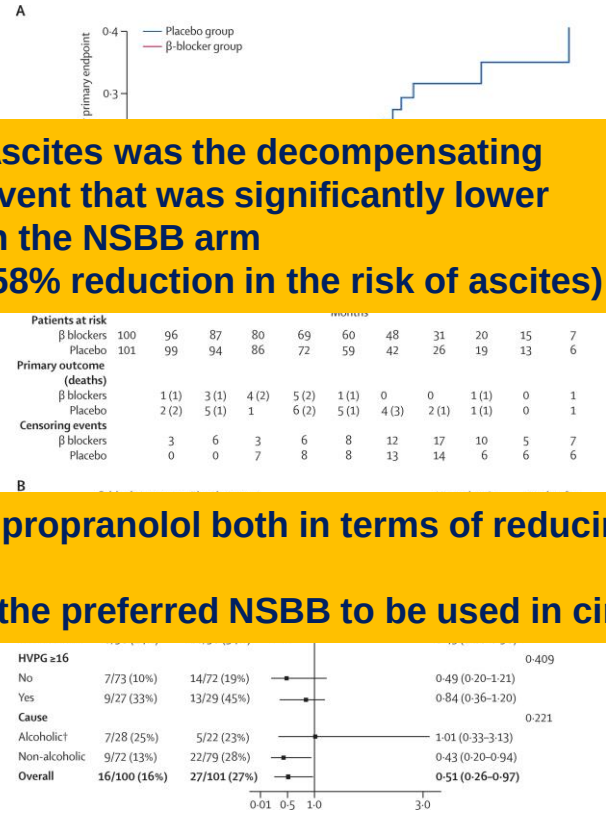


CSPH=Clinically significant Portal HTN; cACLD compensated advanced chronic liver disease.

Beta Blockers to Prevent Decompensation of Cirrhosis in Patients With Clinically Significant Portal Hypertension (PREDESCI): A Randomized, Double-Blind, Placebo-Controlled Multicenter Trial.



NSBBs were associated with a significant 49% lower risk of decompensation compared with placebo.

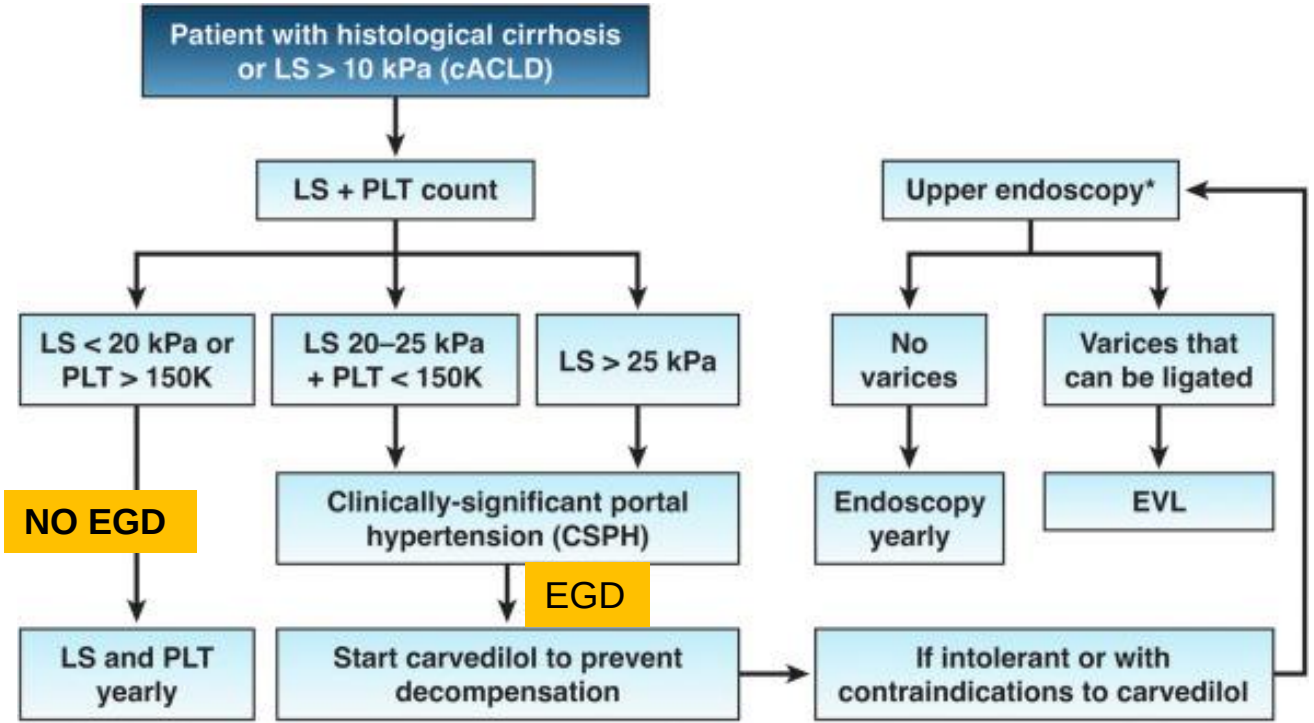


Ascites was the decompensating event that was significantly lower in the NSBB arm (58% reduction in the risk of ascites)

Post hoc analysis showed that carvedilol outperformed propranolol both in terms of reducing portal pressure and in preventing decompensation.
Baveno consensus statement that carvedilol should be the preferred NSBB to be used in cirrhosis

Villanueva C. Albillos A. Genesca J. *Lancet.* 2019; 393: 1597-1608; Bosch J. Garcia-Tsao G. **Baveno VII - renewing consensus in portal hypertension.** *J Hepatol.* 2022; **76**: 959-974.

Initiation of Beta Blockers and Variceal Screening in Compensated Cirrhosis



LS: Liver Stiffness.

Abraldes J.G et al **Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: the "Anticipate" study.** *Hepatology.* 2016; **64**: 2173-2184; Rabiee A. et al **Noninvasive predictors of clinically significant portal hypertension in NASH cirrhosis: validation of ANTICIPATE models and development of a lab-based model.** *Hepatol Commun.* 2022; **6**: 3324-3334.

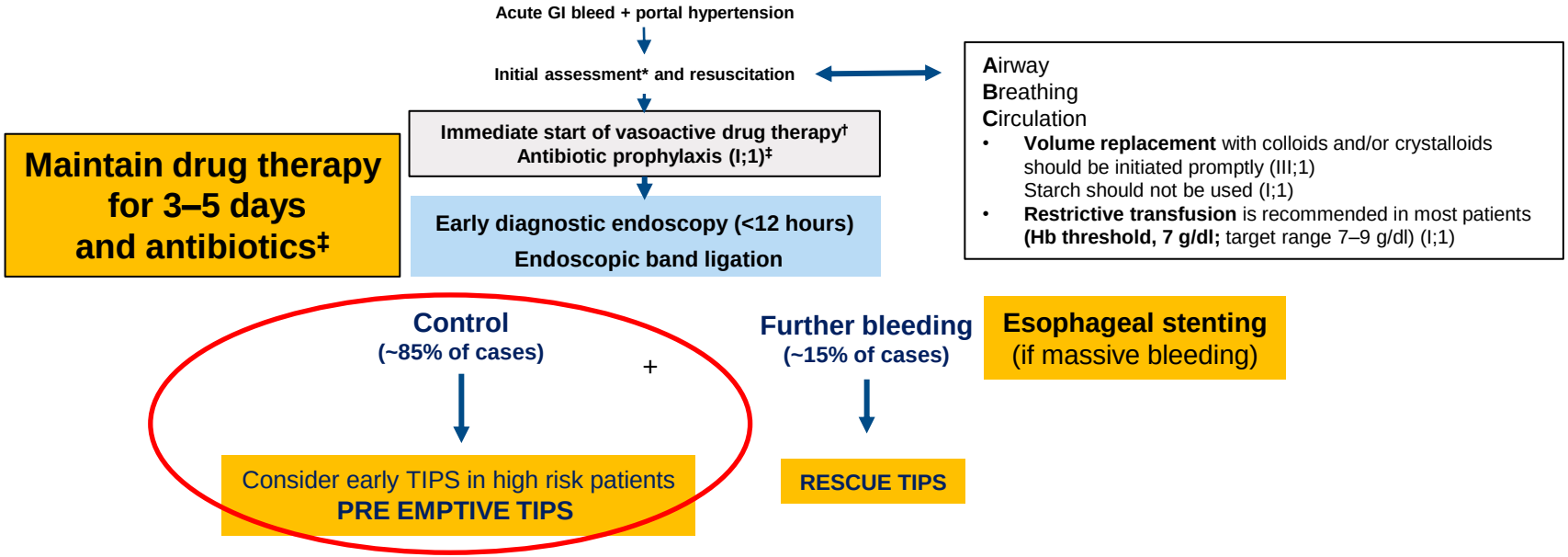
Prevention of a First Variceal Hemorrhage in Patients With Decompensated Cirrhosis: When to Start

1. Patients with decompensated cirrhosis an upper endoscopy still is indicated in all cases.
2. Small varices in decompensated cirrhosis carry the same risk of bleeding as large varices in compensated cirrhosis.
3. In patients with ascites NSBBs may be used to prevent first variceal hemorrhage in varices of any size
4. Considering the greater portal pressure–reducing effect[1] and the easier titration, carvedilol is preferred in cirrhosis.

de Franchis R. Bosch J. Garcia-Tsao G. et al. **Baveno VII - renewing consensus in portal hypertension.** *J Hepatol.* 2022; **76**: 959-974

Variceal Haemorrhage: Management of Acute GI Bleeding

- **Medical emergency**: high rate of complications and mortality in DC
  - Requires immediate treatment and close monitoring



*History, physical and blood exam, cultures; †Somatostatin/terlipressin; ‡Ceftriaxone (1 g/24 hours) is the first choice in patients with DC, those already on quinolone prophylaxis, and in hospital settings with high prevalence of quinolone-resistant bacterial infections. Oral quinolones (norfloxacin 400 mg BID) should be used in the remaining patients (I;1)
Figure adapted from de Franchis R et al. *J Hepatol.* 2015;63:743–52; EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024.

“Preemptive TIPS” in High Risk of Rebleeding

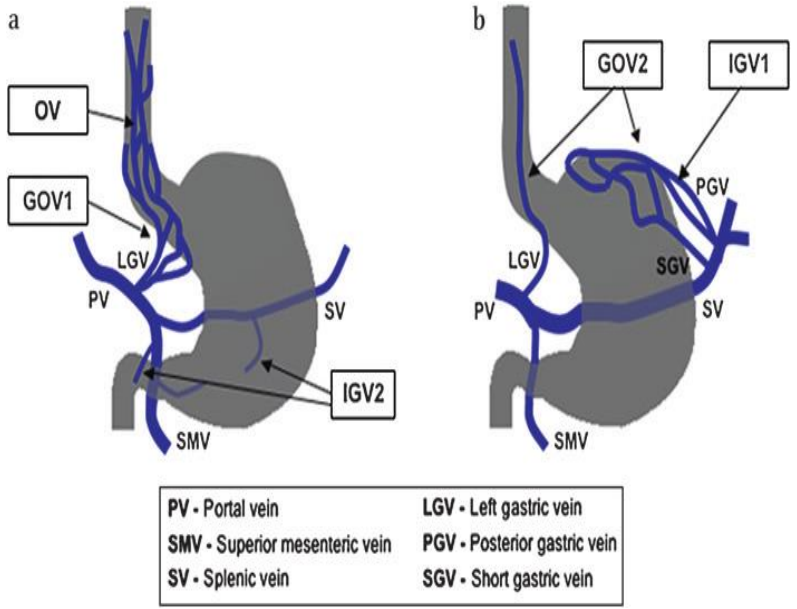
1. **Child-Turcotte-Pugh (CTP) class B cirrhosis with active bleeding during endoscopy**
2. **CTP class C (with a score <13),**

- Improve 1-year survival,
- Reduce treatment failure
- May Improve transplant-free survival

Yang Z, Liu L, et al. Early TIPS with covered stents versus standard treatment for acute variceal bleeding in patients with advanced cirrhosis: a randomised controlled trial. *Lancet Gastroenterol Hepatol.* 2019; 4: 587-598; García-Pagán JC, Caca K, Bureau C, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. *N Engl J Med.* 2010; 362: 2370-2379; Dunne PDJ, Sinha R, Stanley AJ, et al. Randomised clinical trial: standard of care versus early-transjugular intrahepatic porto-systemic shunt (TIPSS) in patients with cirrhosis and oesophageal variceal bleeding. *Aliment Pharmacol Ther.* 2020; 52: 98-106.

Treating Bleeding Gastric Varices

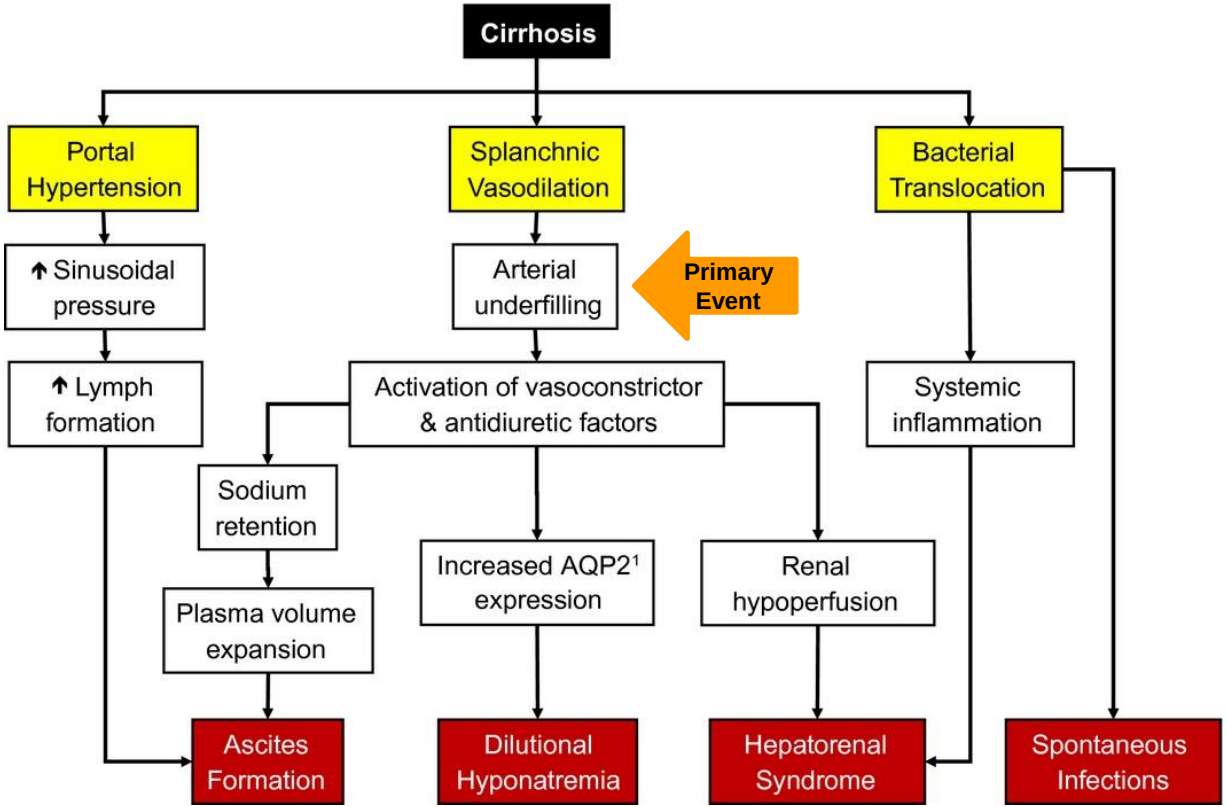
- GOV 1 (those extending into the lesser curvature) same as esophageal varices.[8]
- **Gastrofundal varices (GOV2, IGV 1)** defined as varices in the fundus with extension into the esophagus (gastroesophageal varices type 2) or without extension into the esophagus (isolated gastric varices type 1) have a specific vascular anatomy and distinct management
- **First-line endoscopic treatment is cyanoacrylate injection (lower risk for bleeding vs banding) ? EUS guided coils**
- **TIPS is effective, although usually requires variceal embolization**,



- Henry Z.
- Patel K. Patton H. et al.

AGA clinical practice update on management of bleeding gastric varices: expert review.
Clin Gastroenterol Hepatol. 2021; **19**: 1098-1107.

Why Ascites


Cirrhosis
Portal Hypertension
Splanchnic Vasodilation
Bacterial Translocation
↑ Sinusoidal pressure
Arterial underfilling
Primary Event
↑ Lymph formation
Activation of vasoconstrictor & antidiuretic factors
Systemic inflammation
Sodium retention
Increased AQP2[1] expression
Renal hypoperfusion
Plasma volume expansion
Ascites Formation
Dilutional Hyponatremia
Hepatorenal Syndrome
Spontaneous Infections

Uncomplicated Ascites: Prognosis

- 1-year mortality: 40% 2-year mortality: 50%
- Patients with ascites should be considered for referral for LT
- Patients may not receive adequate priority in transplant lists
- Most commonly used prognostic scores can underestimate mortality risk
- Improved methods to assess prognosis in these patients are needed (Creatinine and Sodium may offset)

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

Initial Treatment of Ascites

1. Moderate Salt Restriction 5 grams Na+/day (EASL)
"No added Salt" Avoid Salty Food -more practical
AASLD – 2 gms /day – Avoid Nutritional Deficiency

2. **Diuretics** Aldosterone Antagonists (to counter hyperaldosteronism)
Spironolactone at 100 mg (max 400 mg)

3. **Loop Diuretics**
Furosemide at 40 mg max at 160 mg /day
Torsemide and Bumetanide if furosemide is not working
(In patients with CKD Loop may be more effective)

In patients without peripheral edema, weight loss exceeding 0.5 kg (1 lb) per day may result in plasma volume contraction, predisposing the patient to renal failure and hyponatremia

NO Fluid Restriction (unless HypoNatremia)

Chirapongsathorn S. Valentin N. Alahdab F. et al. **Nonselective beta-blockers and survival in patients with cirrhosis and ascites: a systematic review and meta-analysis.** *Clin Gastroenterol Hepatol.* 2016; **14**: 1096-1104.

Refractory Ascites:

Diuretic **resistant**

Lack of response to Sodium restriction and diuretic treatment

TIPS

Diuretic intractable

development of diuretic-induced complications

(Long Term Albumin Infusion)

Liver Transplantation
Living Donor if MELD is low

Consider stopping beta blockers
High Risk of Hepatorenal syndrome

Riggio O. Angeli P. **Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial.** *Lancet.* 2018; **391**: 2417-2429; EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024; Chirapongsathorn S. Valentin N. Alahdab F. et al. **Nonselective beta-blockers and survival in patients with cirrhosis and ascites: a systematic review and meta-analysis.** *Clin Gastroenterol Hepatol.* 2016; **14**: 1096-1104.

Refractory Ascites: Indications for TIPS

- TIPS decompresses the portal system*
  - **Short term:** accentuates peripheral arterial vasodilation
  - **Within 4–6 weeks:** improves effective volaemia and renal function to increase renal sodium excretion

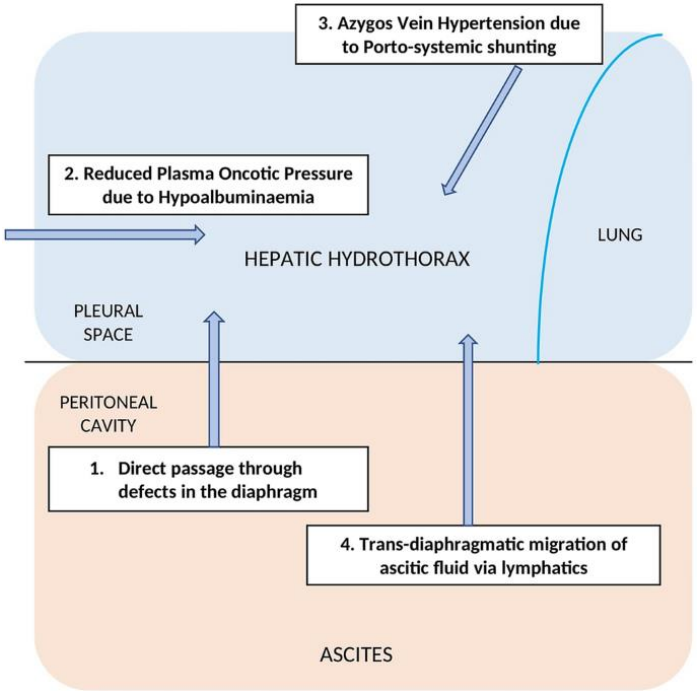
Patients should be **evaluated for TIPS** insertion when: • There is **refractory or recurrent ascites** • Paracentesis is ineffective
TIPS insertion is recommended in patients: • **With 'recurrent ascites' as it improves survival** • With **refractory ascites** as it improves the control of ascites
The use of **small-diameter PTFE-covered stents** is recommended to reduce the risk of TIPS dysfunction and hepatic encephalopathy
After TIPS insertion, continue the following until ascites resolution: • Diuretics and salt restriction • Close clinical follow-up

*By shunting an intrahepatic portal branch into a hepatic vein.

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

Hepatic hydrothorax: Definition and Diagnosis

- **Definition**
  - **Accumulation of transudate in the pleural space**
    - **In the absence of cardiac, pulmonary or pleural disease**
    - **ECHO/CT Chest/Right Heart Cath**
    - **Median survival: 8–12 months**



*Grade of evidence III, grade of recommendation 1

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

Hepatic Hydrothorax: Beyond Diuretics and Thoracentesis

- Patients with hydrothorax should be evaluated for LT (irrespective of MELD score)
- Diuretics and thoracentesis are recommended as the first-line management of hepatic hydrothorax
- **Chronic pleural drainage should <u>not</u> be performed** because of the frequent occurrence of complications

TIPS insertion is first line RX

Living Donor Liver Transplantation (if MELD not high)

Pleurodesis

Mesh repair of diaphragmatic defects

(The best results are achieved in patients with non-advanced cirrhosis without renal dysfunction)

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

Management of SBP: Primary Prophylaxis

- Patients with cirrhosis and low ascitic fluid protein concentration (<1.0 g/mL) and/or high serum bilirubin levels are at high risk of developing a first episode of SBP[1]

Primary prophylaxis with CIPROFLOXACIN 500 mg recommended in patients with:

1. Child–Pugh score ≥9 and serum bilirubin level ≥3 mg/dl, and
2. Either impaired renal function Cr >1.2 or hyponatraemia, Na < 130 and
3. Ascitic fluid protein lower than 1.5 g/ml
4. Prophylaxis should be stopped after disappearance of ascites

1. Wiest R et al. *Gut.* 2012;61:297–310; EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024.

Management of SBP: Use of Albumin

- In patients with SBP treated with a third generation intravenous cephalosporin antibiotic, albumin significantly decreased the incidence of type-1 hepatorenal syndrome and reduced mortality[1]

The administration of albumin is recommended in patients with SBP

- 1.5 g/kg at diagnosis and
- 1 g/kg on Day 3

1. Sort P et al. *N Engl J Med.* 1999;341:403–9; EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024.

Management of SBP: Secondary Prophylaxis

- In patients who survive an episode of SBP, the cumulative recurrence rate at 1 year is approximately 70%[1]
- Prophylactic Cipro (500 mg/day, orally) is recommended in patients who recover from an episode of SBP
- At present, rifaximin cannot be recommended as an alternative to Cipro for secondary prophylaxis of SBP
- prophylaxis of SBP among patients already on rifaximin for the prevention of recurrent HE
- Patients who recover from SBP have a poor long-term survival and should be considered for LT
- **PPIs may increase the risk for the development of SBP**, their use should be restricted to those with a clear indication

1. Rimola A et al. *J Hepatol.* 2000;32:142–53; EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024.

Prevention of Hepatorenal Syndrome-Acute Kidney Injury in Patients With Cirrhosis

- Avoid NSAIDs
- Avoid ACE inhibitors
- Decrease/withdraw diuretics when decompensated
- Limiting lactulose dose to accomplish 2-3 BMs per day
- Threshold at which to discontinue beta-blockers?
- Maintain mean arterial pressure (MAP)

Tapper EB et al. *Am J Med.* 2016; 129: 461-467.

Earlier Diagnosis Can Lead to Better Outcomes, as Recommended by AASLD Guidance[1-4]

Diagnose at lower SCr levels[5-7]
Baseline creatinine (at the time of therapy initiation) is a well-known predictor of HRS reversal

Maintain appropriate fluid/albumin levels[8]
Over-resuscitation can lead to life-threatening complications

2021 AASLD Guidance for Diagnosis[1]*

All must be present for proper HRS diagnosis[1]:

- ✓ Cirrhosis with ascites
- ✓ *Increase in SCr ≥0.3 mg/dL within 48 hours or ≥50% increase in SCr that is known or presumed to have occurred within the preceding 7 days*
- ✓ Absence of shock
- ✓ *No improvement after 48 hours of diuretic withdrawal and volume expansion with albumin*
- ✓ No current or recent treatment with nephrotoxic drugs
- ✓ Absence of parenchymal kidney disease

SCr, serum creatinine.
*Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Biggins SW, Angeli P, Garcia-Tsao G, Ginès P, Ling SC, Nadim MK, Wong F, Kim WR. Copyright © 2021 American Association for the Study of Liver Diseases. Reproduced with permission of John Wiley & Sons, Inc.

1. Biggins SW et al. *Hepatology*. 2021;74(2):1014-1048. 2. Bera C, Wong F. *Therap Adv Gastroenterol*. 2022;15:1-19. 3. Wong F et al. *J Hepatol*. 2019;70:e692-693. 4. Sanyal AJ et al. *Aliment Pharmacol Ther*. 2017;45(11):1390-1402. 5. Boyer TD et al. *J Hepatol*. 2011;55(2):315-321. 6. Solé C et al. *Liver Int*. 2018;38(11):1891-1901. 7. Piano S et al. *Clin Gastroenterol Hepatol*. 2018;16(11):1792-1800. 8. TERLIVAZ® (terlipressin). Prescribing Information. Mallinckrodt Hospital Products Inc.

Current Treatments of HRS-AKI

Once HRS-AKI is confirmed, treatment consists of IV albumin and a vasoconstrictor

IV Albumin

- 0.5-1 gm/kg (max 100 gm/day) for resuscitation followed by
- 25-50 gm/day (after HRS AKI diagnosis)

Plus a Vasoconstrictor

- Terlipressin (only approved therapy for HRS-AKI)- Does Not Require ICU
- Norepinephrine: Needs ICU
- Midodrine (+/- octreotide) – alpha adrenergic agonist/somatostatin analogue (much less effective)

Terlipressin not effective if Serum Creatinine > 5 mg/dL

Terlipressin (Only Approved Therapy for HRS-AKI)

Prior to and During Treatment, Monitor for Risk of Respiratory Failure in All Patients[1]

Risk factors for respiratory failure[1]	If present prior to initiation[1]	During treatment[1]
Hypoxia (SpO_2 <90%)	Do not initiate until oxygenation levels improve	Discontinue terlipressin
ACLF grade 3	Avoid use due to significant risk of respiratory failure	Avoid use due to significant risk of respiratory failure
Intravascular volume overload	Use caution. Reduce or discontinue the administration of albumin and/or other fluids and judiciously use diuretics	Reduce or discontinue the administration of albumin and/or other fluids and judiciously use diuretics. Temporarily interrupt, reduce, or discontinue terlipressin treatment until patient volume status improves

During CONFIRM, when respiratory failure occurred with terlipressin, it had a median onset of 5 days, an average onset of 7.5 days, and a range of 1 to 67 days.[2]

SpO_2, oxygen saturation.

1. TERLIVAZ® (terlipressin). Prescribing Information. Mallinckrodt Hospital Products Inc. 2. Data on File – Ref-05035. Mallinckrodt Pharmaceuticals.

Please see Indication, Limitation of Use, Important Safety Information, including Boxed Warning, and full Prescribing Information available at this program.

Management of HRS: TIPS and Liver Transplant

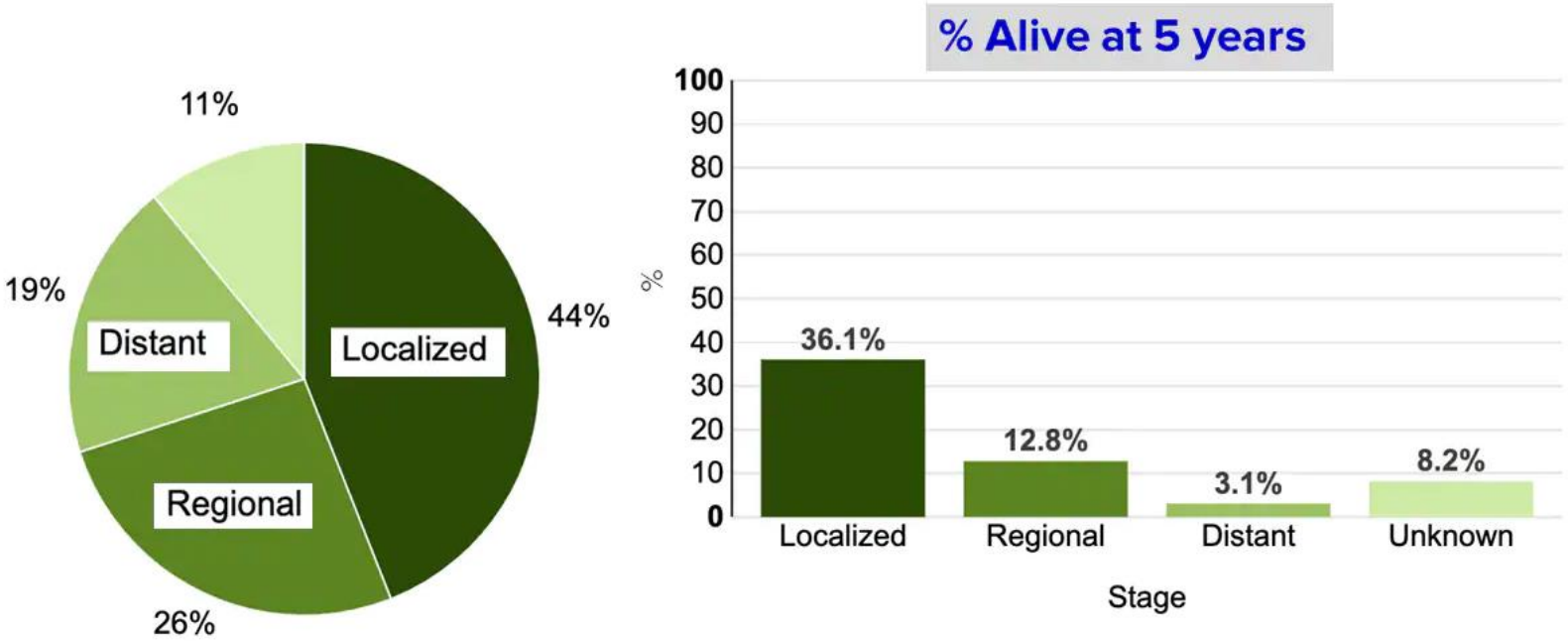
In most patients with HRS-AKI TIPS is contraindicated because of severe degree of liver failure

There is insufficient data to advocate TIPS in HRS-AKI • It could be suggested in selected patients with HRS-NAKI
Liver Transplant is the **best therapeutic option** for patients with **HRS** regardless of the response to drug therapy
The decision to initiate RRT should be based on the individual severity of illness
The indication for **Simultaneous liver-kidney transplantation** • Should be considered in patients with significant CKD (GFR <60ml/min > 3months) or sustained AKI including HRS-AKI (> 6 weeks on HD) with no response to drug therapy

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

Most HCC Detected at Later Stages When Prognosis Is Poor

Data From SEER 17, 2012-2018



NCI. Accessed September 30, 2022. https://seer.cancer.gov/statistics-network/explorer/application.html

HCC Surveillance Is Recommended to Improve Early Detection Rates, but Challenges Exist

~3 million§
patients eligible for surveillance in the USA

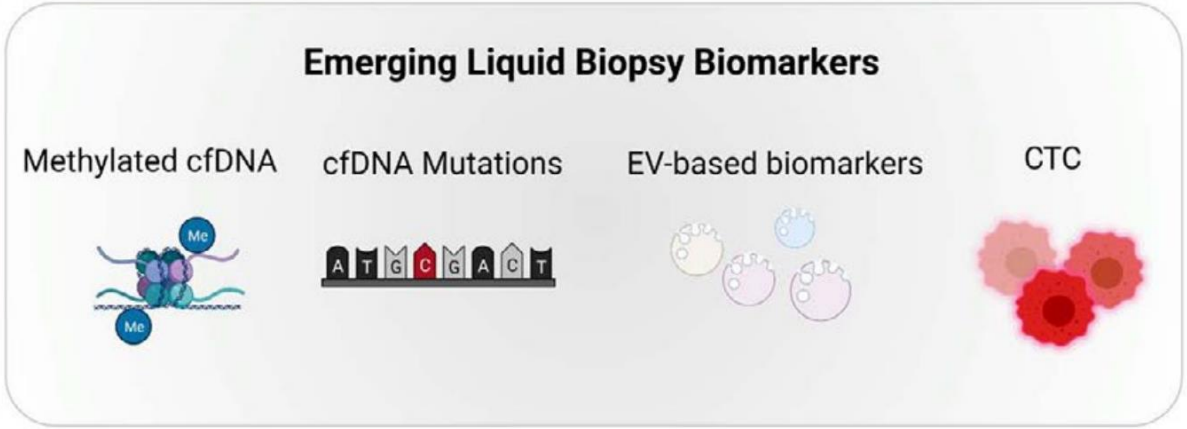
<30% of at-risk patients receive recommended surveillance for HCC[1]

Standard of Care methods provide poor/variable sensitivity for **early-stage disease**[2]

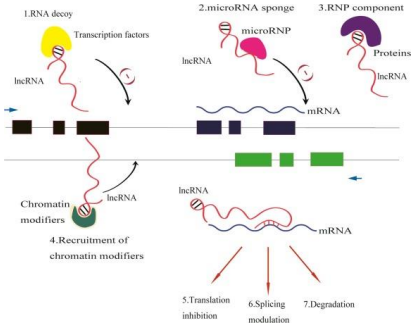
	Sensitivity (early-stage)	Specificity
U/S[2]	47%	92%
AFP[3]	31%	98%
U/S + AFP[2]	63%	84%

1. Wolf E et al. J Hepatology. 2020; § Calculated using US Census Bureau estimates of population and prevalence of cirrhosis in population as reported in Beste et al. *Gastroenterology*. 2015; 2. Tzartzeva K et al.*Gastroenterology*. 2018; 3. Chalasani NP et al. *ASCO*. May 2020, 4577.

Liquid Biopsy Is Encouraging, but Requires Cross Validation and Better Precision



lncRNA



cf: Cell free
EV: extracellular vesicle-based protein: Hepatology 2023 Mar
CTC: circulating Tumor Cells
lncRNA: Long Non Coding RNA

Adeniji and Dhanasekaran. *Hepatology Communications.* 2021.

The Liver Cancer Genetic Test Includes a Blood-Based Test for HCC surveillance

In vitro diagnostic assay to analyze patients' **blood** for the presence of **Methylated DNA Markers** (MDMs) and a **protein biomarker—**yielding qualitative results

Methylated DNA Markers

A class of biomarkers that target aberrant methylation of gene promoter regions

Methylated Markers:
HOXA1, TSPLY5, B3GALT6

Alpha Fetoprotein (AFP)

Elevated serum AFP levels have been observed in several malignant diseases, including HCC

Intended Patient Population

The Liver Cancer Genetic Test is indicated as an aid in the detection of HCC for adults with liver cirrhosis and/or chronic hepatitis B (HBV) who are at an increased risk for HCC.

Biomarkers for Early Detection Vary in Performance and Readiness

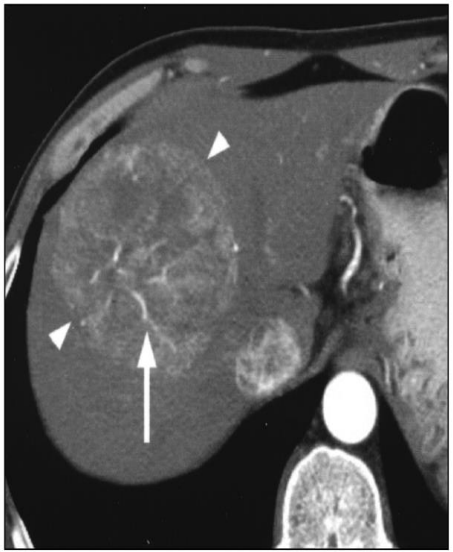
Test	EDRN phase of validation	Performance characteristics	
US plus AFP	**5**	Sensitivity Specificity	61% 92%
AFP-L3%	**3**	Sensitivity Specificity	62% 90%
DCP	**3**	Sensitivity Specificity	40% 81%
Multitarget algorithm	**2**	Sensitivity Specificity	82% 87%
GALAD	**2/3**	Sensitivity Specificity	54–72% 90%
Doylestown plus	**2/3**	Sensitivity Specificity	90% 95%

- US, ultrasound
- AFP-L3%, *Lens culinaris* lectin binding subfraction of AFP
- DCP, des-gamma carboxyprothrombin
- Multitarget algorithm: information from 3 **methylation markers** (*HOXA1*, *TSPYL5*, *B3GALT6*), AFP, and **patient sex**
- GALAD: **gender**, **age**, AFP-L3%, AFP, and DCP
- Doylestown Plus: **age**, logAFP, PEG-precipitated IgG, and **fucosylated kininogen**

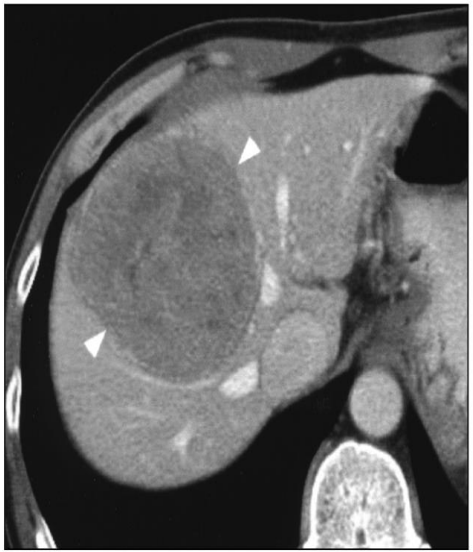
Parikh et al. *Cancer Epidemiol Biomarkers Prev*. 2020

HCC Diagnosis

- Confirmatory Test is triple phase CT or MRI
- Biopsy is not usually required for a diagnosis of “classical HCC” (LiRad 5) on imaging
- Any other solid lesion in Cirrhosis needs a biopsy

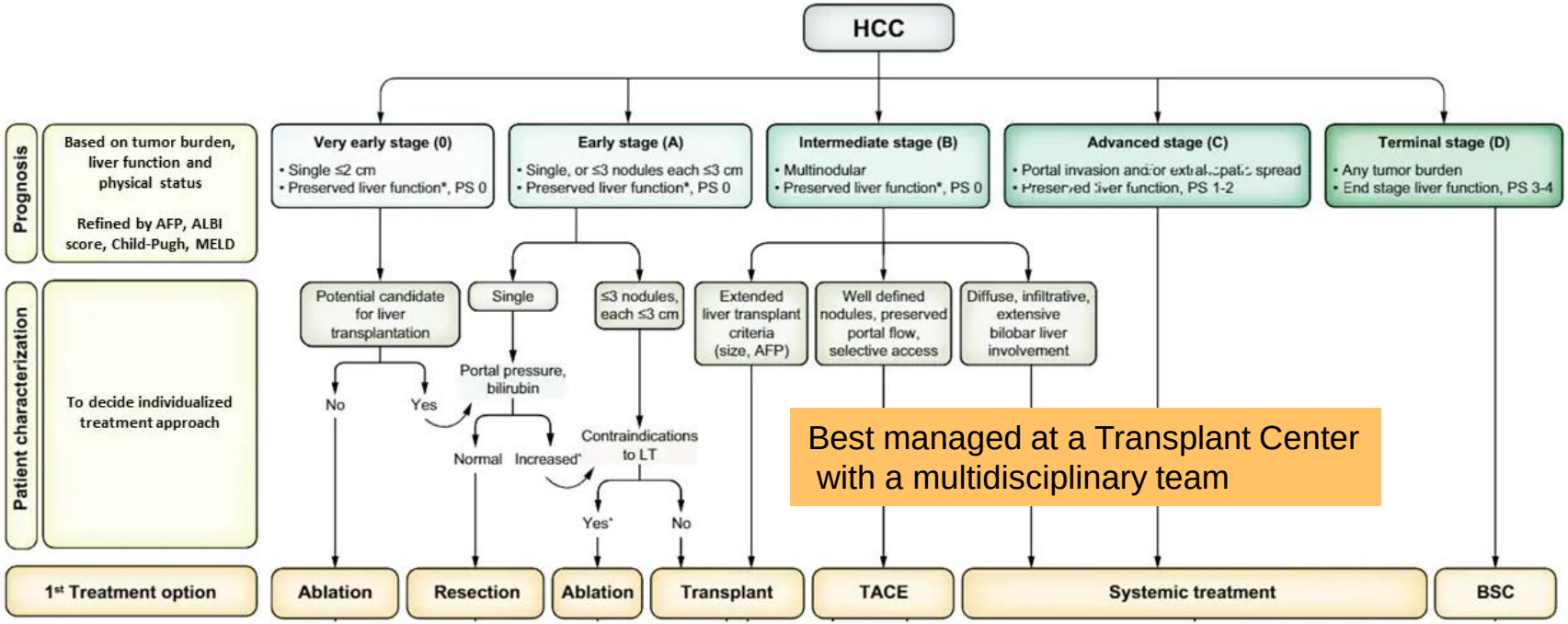


Enhancement



Wash out

BCLC 2022 Staging and Treatment Allocation Update



ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; MELD, model of end stage liver disease; PS, performance status; TACE, transarterial chemoembolization.

Reig M, et al. J Hepatol. 2022;76:681-693.

Liver Transplantation for HCC

- Rx liver disease/failure and cure HCC
- Specific criteria to get MELD exception (One lesion < 5 cm or three max 3 cm)
- Living Donor Transplantation is an option if patient does not meet criteria
- Large HCC (> 5cm or multiple lesions) Radio embolization and Immunotherapy many patients can be down staged and may become eligible for transplant

HIMALAYA Trial
Patients who are not candidates
for Liver TX or loco regional RX

STRIDE Regimen
CTLA-4i induction with PDL1 inhibition
4 year survival of Advanced HCC is 36%

Acute-on-Chronic Liver Failure

- Frequent occurrence in cirrhotic patients
  - 30% of admitted patients and 25% of outpatients
- Major cause of death in patients with cirrhosis (50% mortality rate)
- Characterized by hepatic and extrahepatic organ failure, highly activated systemic inflammation and a high 28-day mortality
- Precipitating events vary between populations and may include:
  - Bacterial infections (30–57% of cases)
  - Active alcohol intake or alcohol binge
  - Reactivation of HBV
  - Superimposed HAV and HEV infection

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

EASL-CLIF Prognostic and Diagnostic Scores for ACLF

CLIF-C ACLF score for mortality prediction[1]*
10 x [0.033 x Clif OFs + 0.04 x Age + 0.63 x Ln(WBC) – 2]

Chronic liver failure – organ failure score system[1]			
Organ/system†	**1 point**	**2 points**	**3 points**
Liver (bilirubin, mg/dl)	<6	≥6–<12	≥12.0
Kidney (creatinine, mg/dl)	<2.0	≥2.0–<3.5	≥3.5 or renal replacement
Brain/HE (West Haven Criteria)	Grade 0	Grades 1–2	Grades 3–4‡
Coagulation (INR, PLT count)	<2.0	≥2.0–<2.5	≥2.5
Circulation (MAP, mmHg and vasopressors)	≥70	<70	Use of vasopressors
Lungs PaO_2/FiO_2, or	>300	≤300–>200	≤200§
SpO_2/FiO_2	>357	>214–≤357	≤214§

*Age in years, creatinine in mg/dL, WBC in 10^6 cells/L, sodium in mmol/L;
†Bold text indicates the diagnostic criteria for organ failures; ‡Patients submitted to mechanical ventilation due to HE and not to a respiratory failure were considered as presenting a cerebral failure (cerebral score = 3); §Other patients enrolled in the study with mechanical ventilation were considered as presenting a respiratory failure (respiratory score = 3)

1. Jalan R et al. *J Hepatol.* 2014;61:1038–47

Management of ACLF

- The cause of liver injury can be treated in certain situations, e.g. HBV
- Early action is crucial to patient survival
  - Treatment of precipitating factors
  - Organ Specific Rx

Early identification and treatment of precipitating factors of ACLF

However, in some patients ACLF progresses despite treatment of precipitating factors

Early referral of patients with ACLF **to LT centres** for immediate evaluation is recommended

Withdrawal of intensive care support after 1 week can be suggested in patients who are not LT candidates and have ≥4 organ failures

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

When Do You Refer for Liver Transplantation?

- Any decompensating Event : (MELD does not matter)
- Liver Transplant Wait listing process takes 2–3 months
- Living Donor Eligibility
- Listed patient easier access in case of ACLF/HRS

Summary

- Liver Stiffness Measurement > 20 is suggestive of Clinically Significant Portal HTN is widely accepted
- Carvedilol is the preferred betablocker and recommended in patients with CSPH
- Early use of TIPS in variceal bleeding and Recurrent Ascites improves survival
- New markers for Detection of HCC are available
- Telripressin is the preferred treatment for HRI AKI
- Living Donor Transplant is a viable option for patients who suffer from complications and low MELD