THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Hepatology Updates Impacting Liver Transplantation

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Disclosures

- No financial disclosures

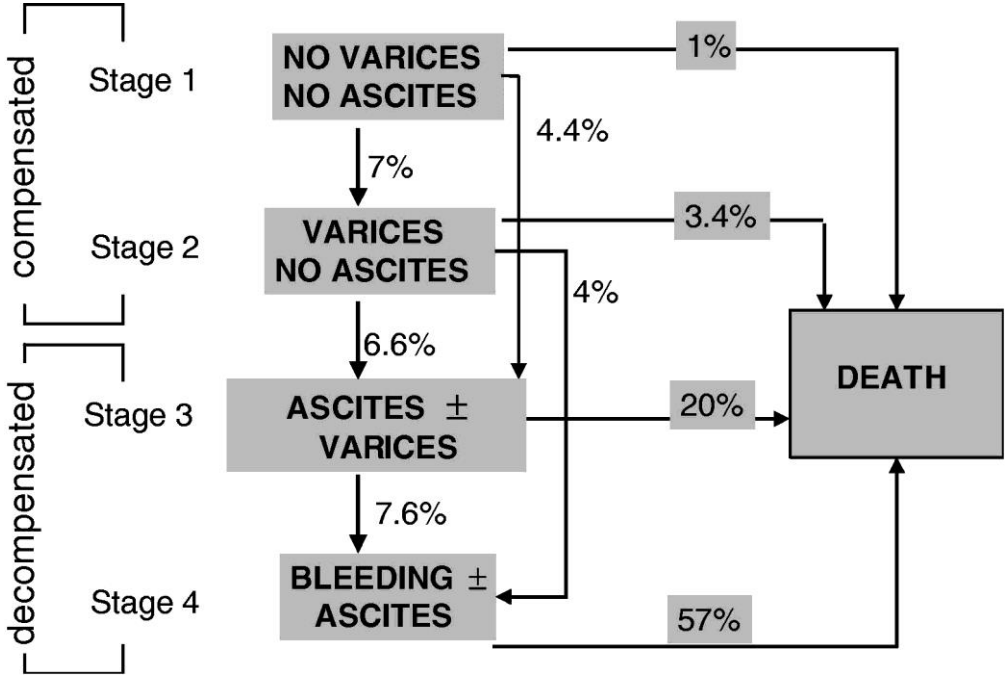
- Will discuss an off-label procedure – treating gastric varices with cyanoacrylate (approved at OSUWMC)

Lecture Objectives / Outline

- Review medical advances impacting liver transplantation
  - Referral timing (MELD; Frailty Assessment; HCC)
  - Endoscopic interventions
  - Steatotic liver disease
  - Hepatorenal Syndrome

Decompensated cirrhosis is greatest predictor of mortality

- Decompensating events include:
  - Ascites
  - Variceal hemorrhage
  - Hepatic encephalopathy
  - Jaundice
- 5-year survival in decompensated cirrhosis around 50%



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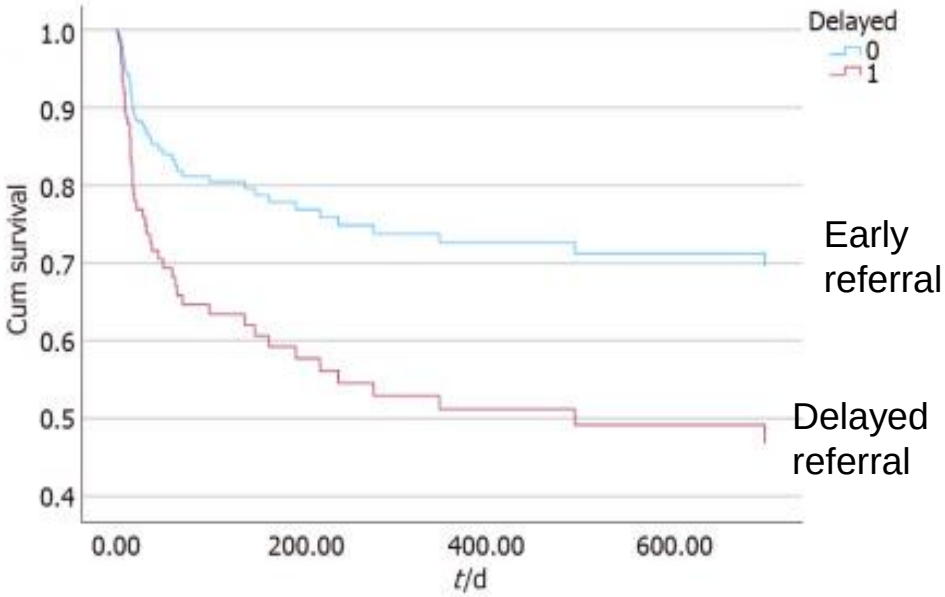
Where does MELD come in?

- MELD (Model for End stage Liver Disease)
  - Predicts 90-day mortality in decompensated cirrhosis
  - Allocation of deceased donor livers
- Original MELD included creatinine, total bilirubin, and INR
  - Adopted by OPTN in 2002
- Updated to include sodium (MELD-Na) in 2016
- Began using **MELD 3.0** in 2023
  - Added albumin and female gender
- Traditionally, there has been a suggested cutoff of 15

The “window” for transplant evaluation

- Late referral for LT is associated with higher mortality
- Cooper et al (2023)
  - Delayed vs. early (within 3 months of decompensation) referrals for LT
  - Patients with early referral had survival benefit
  - No difference in distance to transplant center



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Frailty in End Stage Liver Disease

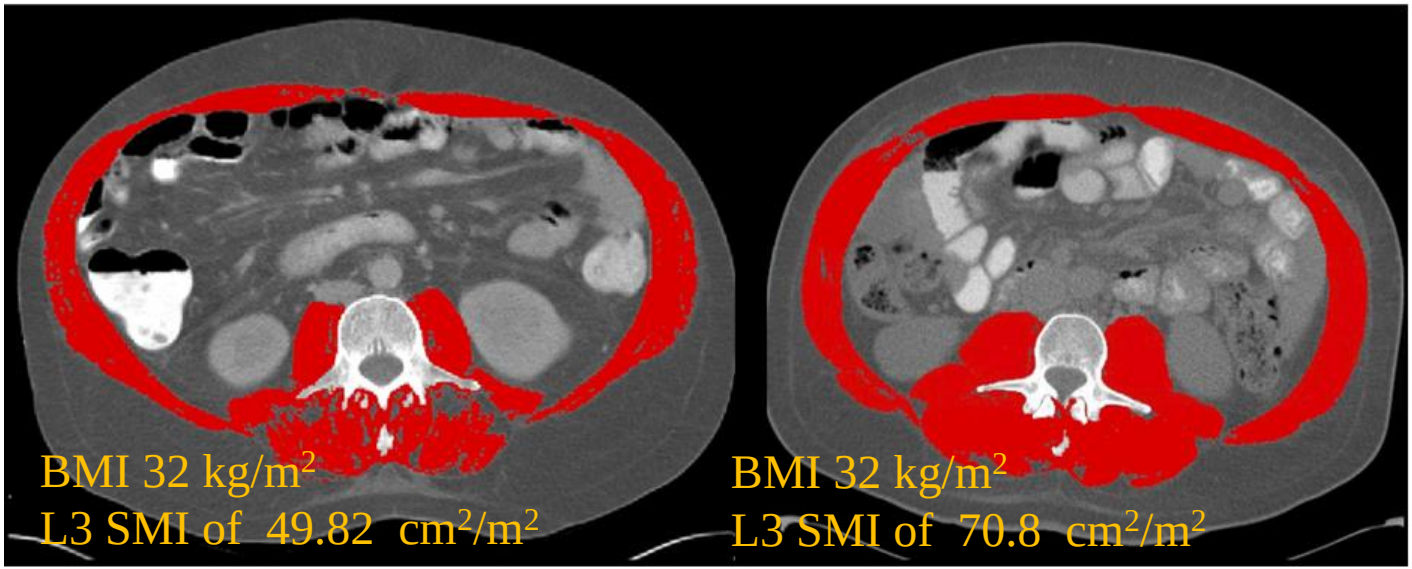
Frailty is associated with increased hospitalizations, longer length of hospital stays, transplant delisting and increased waitlist mortality.

The **Liver Frailty Index (LFI)** was developed to objectively document frailty in an outpatient setting.

The LFI is composed of 3 performance-based variables: hand grip strength, chair stands, and balance. Takes less than 10 minutes to administer.

Outperforms the subjective clinician assessment and MELD score in predicting waitlist mortality and post-LT morbidity.

Sarcopenia assessed via CT scan



Red color indicates skeletal muscles:
rectus abdominis, oblique and lateral abdominal muscles, psoas, and paraspinal muscles.

Montano-Loza et al CHG 2012

Assessment of Frailty

6 Minute walk test

Neuromotor coordination

Robust	Prefrail	Frail
>450 m	450-250 m	< 250 m

LIVER FRAILTY INDEX

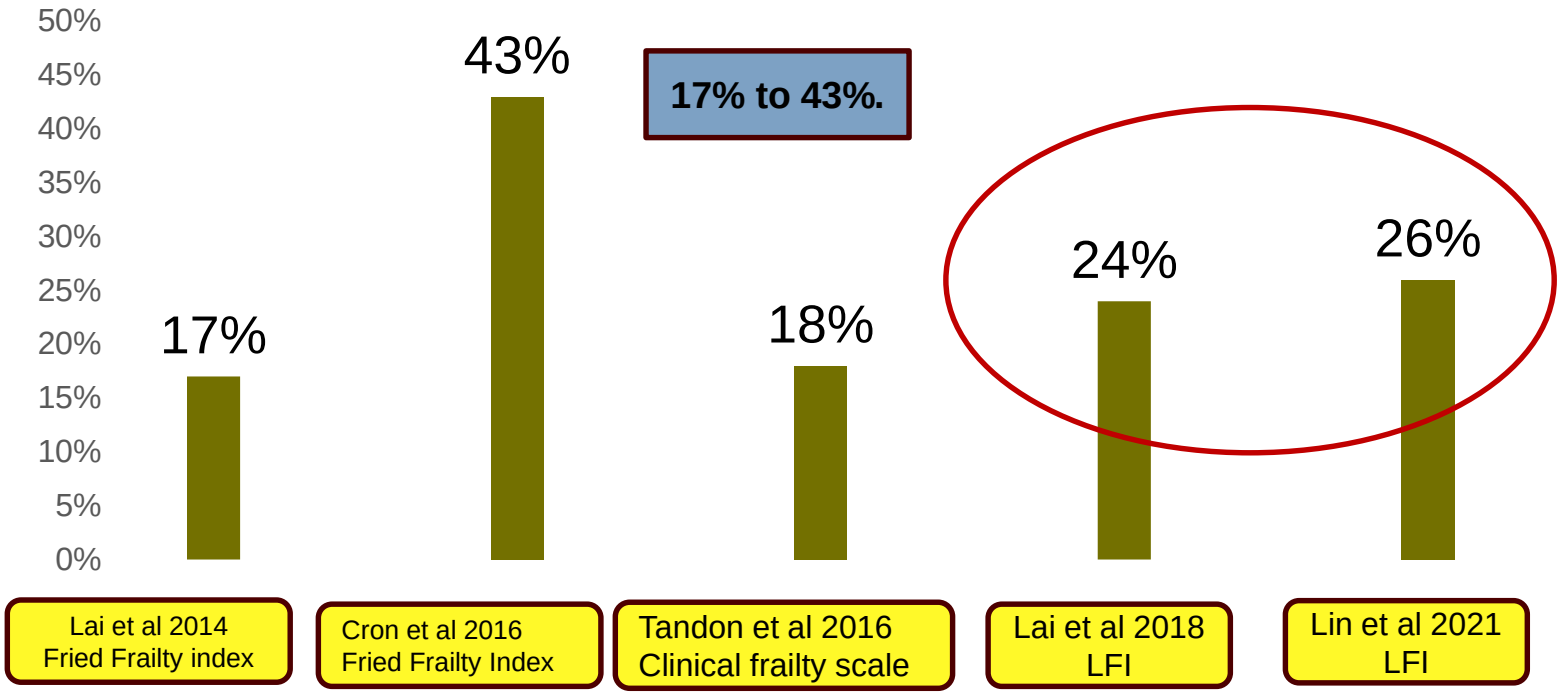
Muscle strength

Nutrition

Robust	Prefrail	Frail
<3.2	3.3-4.4	≥ 4.5

Kardashain et al Hepatology 2021, Carey et al Liver transplantation 2010

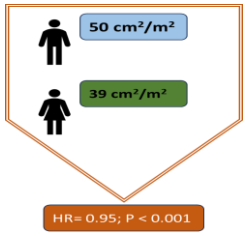
Variable prevalence of Frailty until LFI



46 year old woman admitted for altered mentation and jaundice. Patient is discharged

Now being worked up for liver transplant as outpatient

SMI: 43 cm^2/m^2



Liver Frailty Index™

Inputs: For instructions, see ⓘ below.

1. Gender:
○ Male ◉ Female

2. ⓘDominant hand grip strength (kg):

attempt 1:	attempt 2:	attempt 3:	Avg:	
3.25	3.5	3.5	3.42	kg

3. ⓘTime to do 5 chair stands:
0 sec

4. ⓘSeconds holding 3 position balance:

Side:	SemiTandem:	Tandem:	Total:	
10	6	2	18.00	sec

Results: refresh results

The Liver Frailty Index™ is **6.24**.

Decimal precision: 2

Based on suggested cut-offs of the Liver Frailty Index™, a patient with this Liver Frailty Index™ score is considered **Frail**.

This Liver Frailty Index™ score falls within the **100** percentile of outpatients with cirrhosis who are listed for liver transplantation.

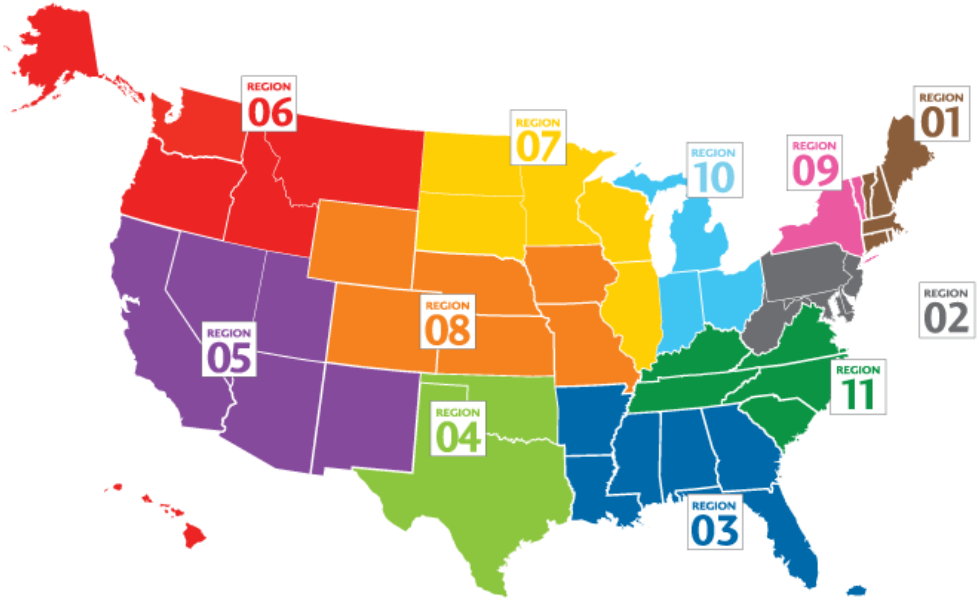
Robust	Prefrail	Frail
<3.2	3.3-4.4	≥ 4.5

6MWT: 400 m

Robust	Prefrail	Frail
>450 m	450-250 m	< 250 m

MELD Exception Points

- MELD exceptions are based on the Median MELD at Transplant (MMaT) from the donor hospital
  - MMaT differs regionally and based on blood type
- Patient with a low “native MELD” can benefit



Hepatocellular Carcinoma

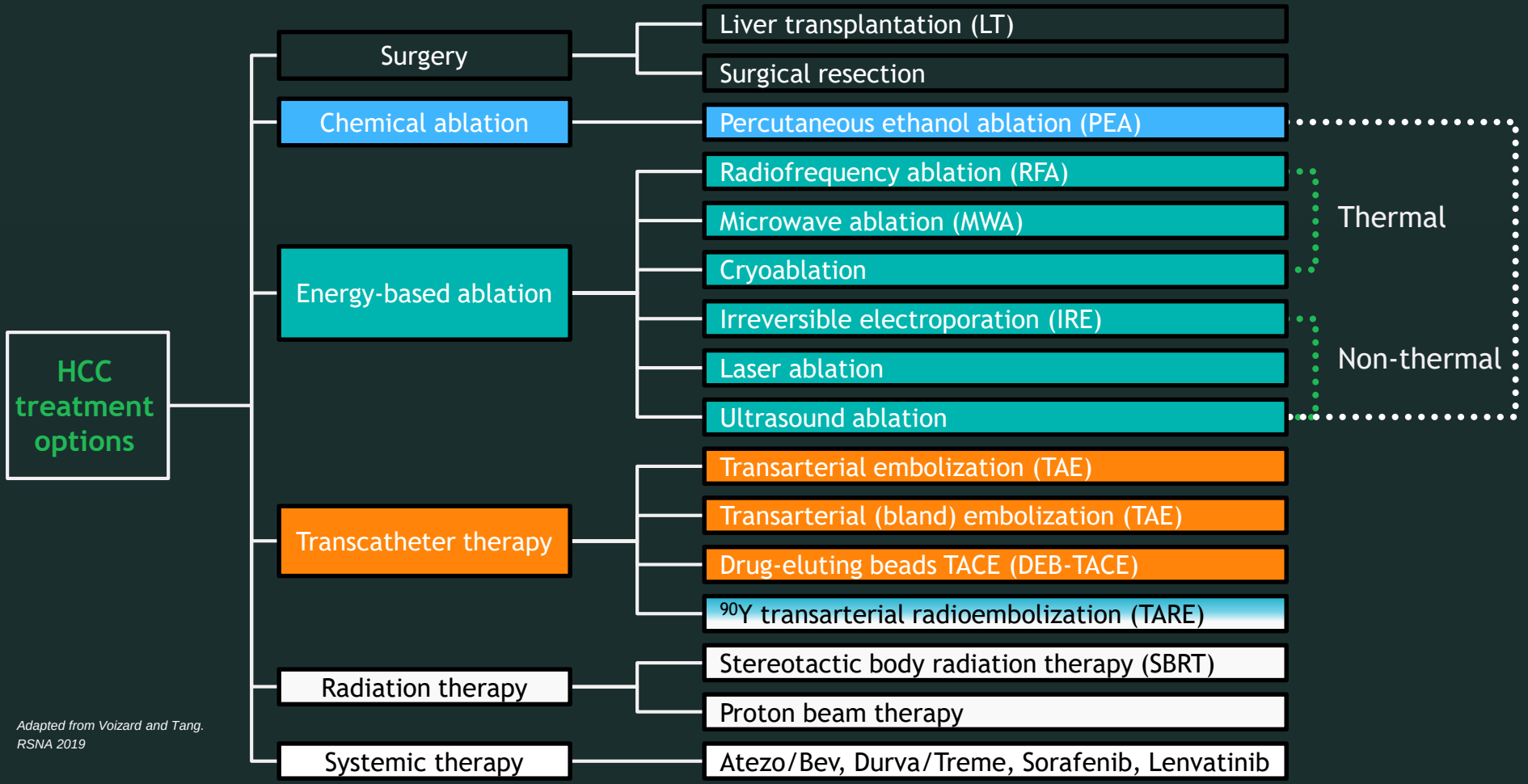
- 6th leading cause of cancer-related death in the US; 5-year survival below 20%
- Most common indication for MELD exception
- Screen with US and AFP Q6 mos in patients with cirrhosis
- Patients do not qualify for MELD exception with:
  - Macrovascular invasion
  - Distant metastases
  - Ruptured HCC
- Refer any patient with HCC to a transplant center

PMID: 32319693

Other Malignancies

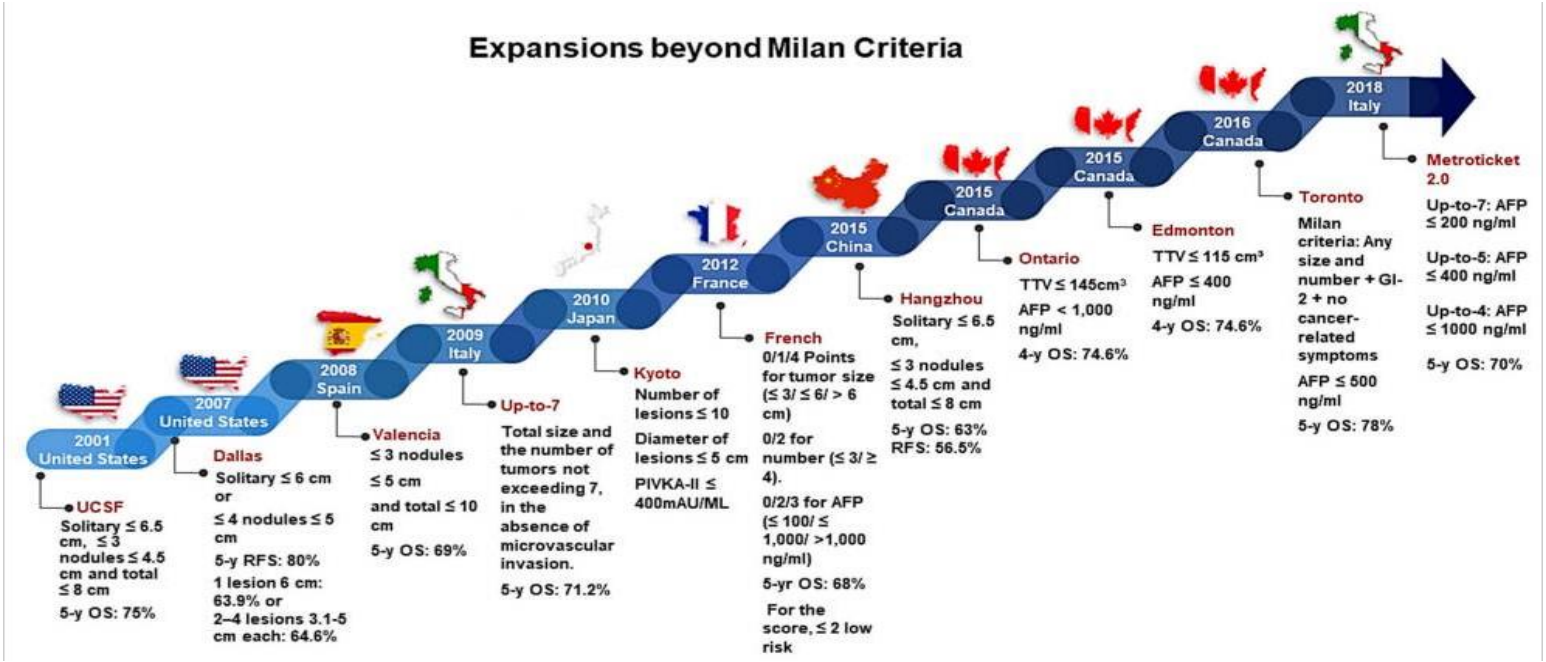
- Cholangiocarcinoma (CCA)
  - Standardized MELD exception
  - Unresectable hilar CCA with neoadjuvant chemoradiation and operative staging
- Neuroendocrine tumors
  - Gastro-endo-pancreas origin
  - Metastases confined to the liver
  - Less then 50% of total liver volume
- Proposed exceptions (2024)
  - Metastatic colorectal cancer
  - Intrahepatic cholangiocarcinoma

OPTN
ORGAN PROCUREMENT AND TRANSPLANTATION NETWORK



Adapted from Voizard and Tang. RSNA 2019

Pushing the Boundaries for HCC: Beyond the Milan Criteria



Abdelrahim M, Esmail A,Transplant Oncology: An Emerging Discipline of Cancer Treatment. Cancers (Basel). 2023 Nov

Post Transplant Recurrence

Morphology and Biology

Size

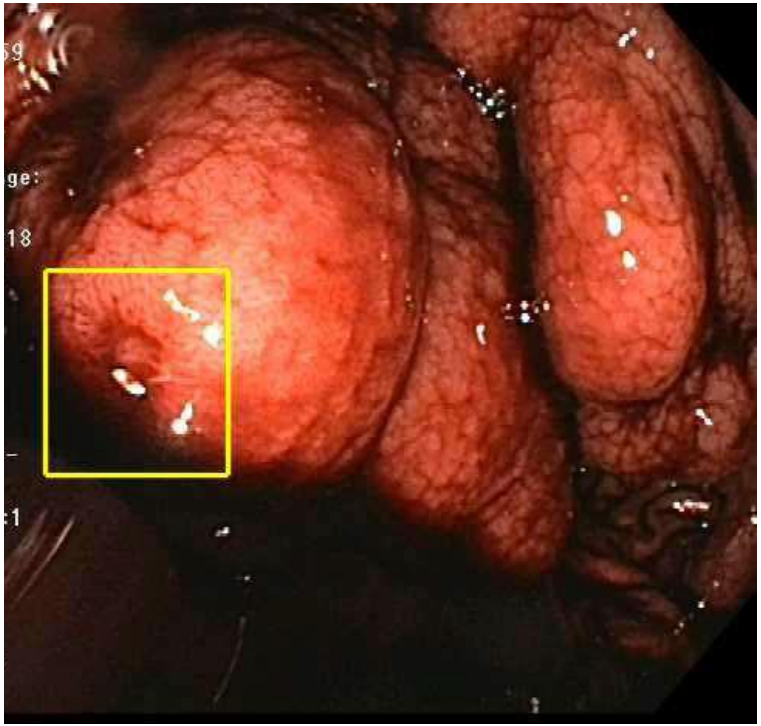
GI bleeding – A messy business

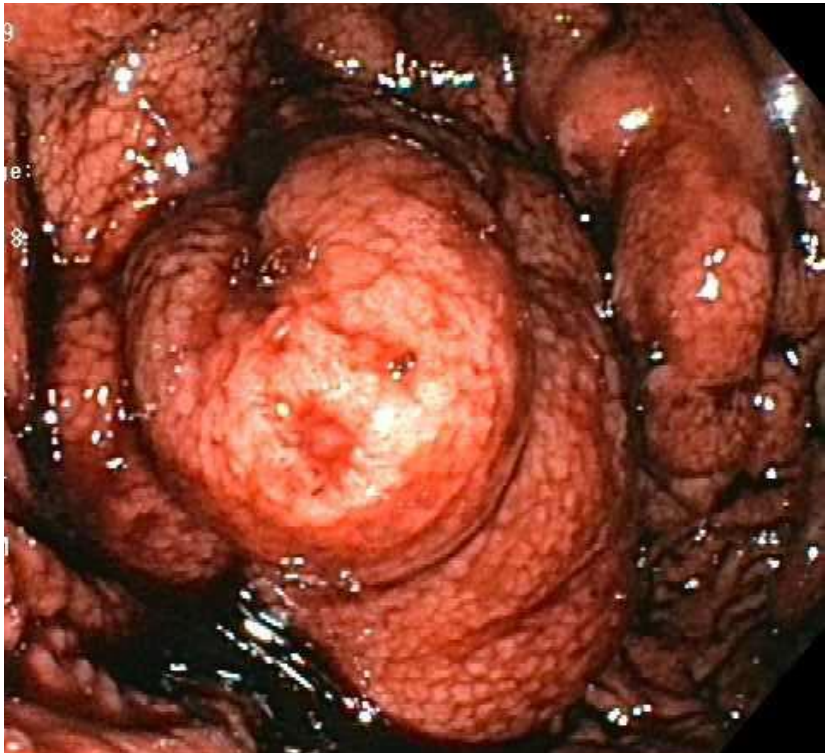
Variceal hemorrhage in the stomach

- **Cyanoacrylate** injection superior to both variceal band ligation and sclerotherapy using alcohol
- Other sclerosants used in the esophagus – sodium tetradecyl sulfate, sodium morrhuate, **ethanolamine** oleate, absolute alcohol

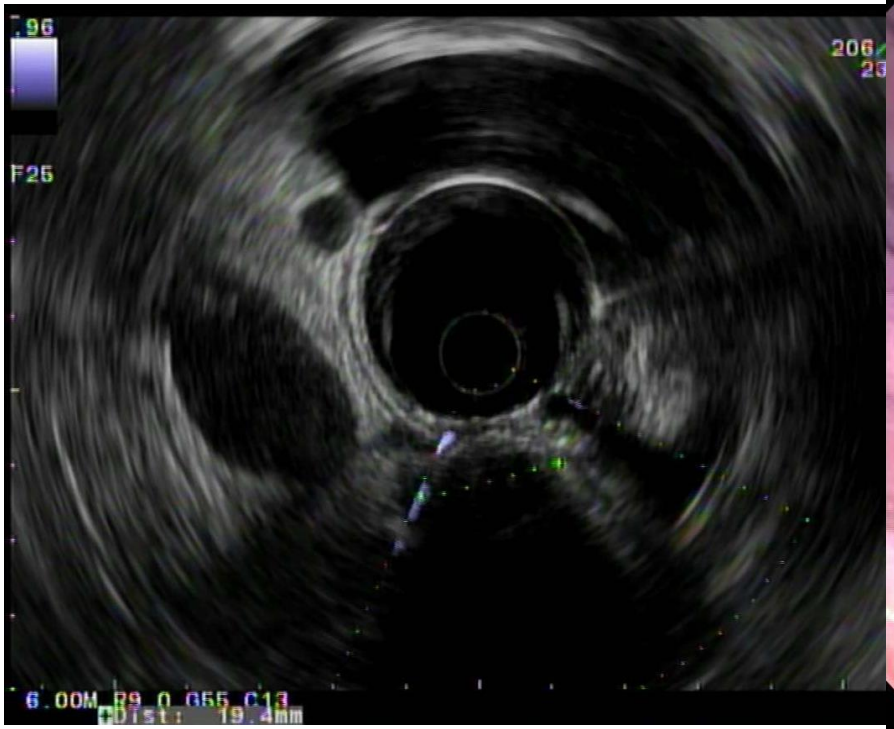
- Complications – bacteremia and variceal ulceration; pulmonary and cerebral emboli have been reported, often due to large portosystemic or pulmonary shunts

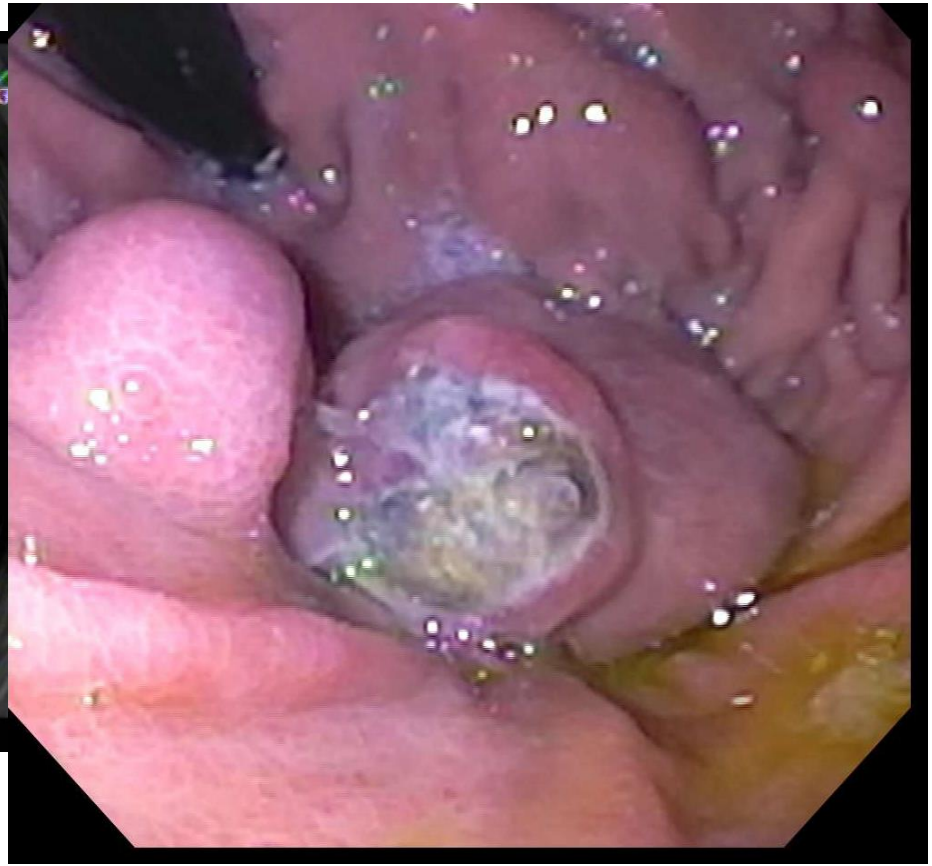
Gastric variceal hemorrhage case
Case 1 – POD 0



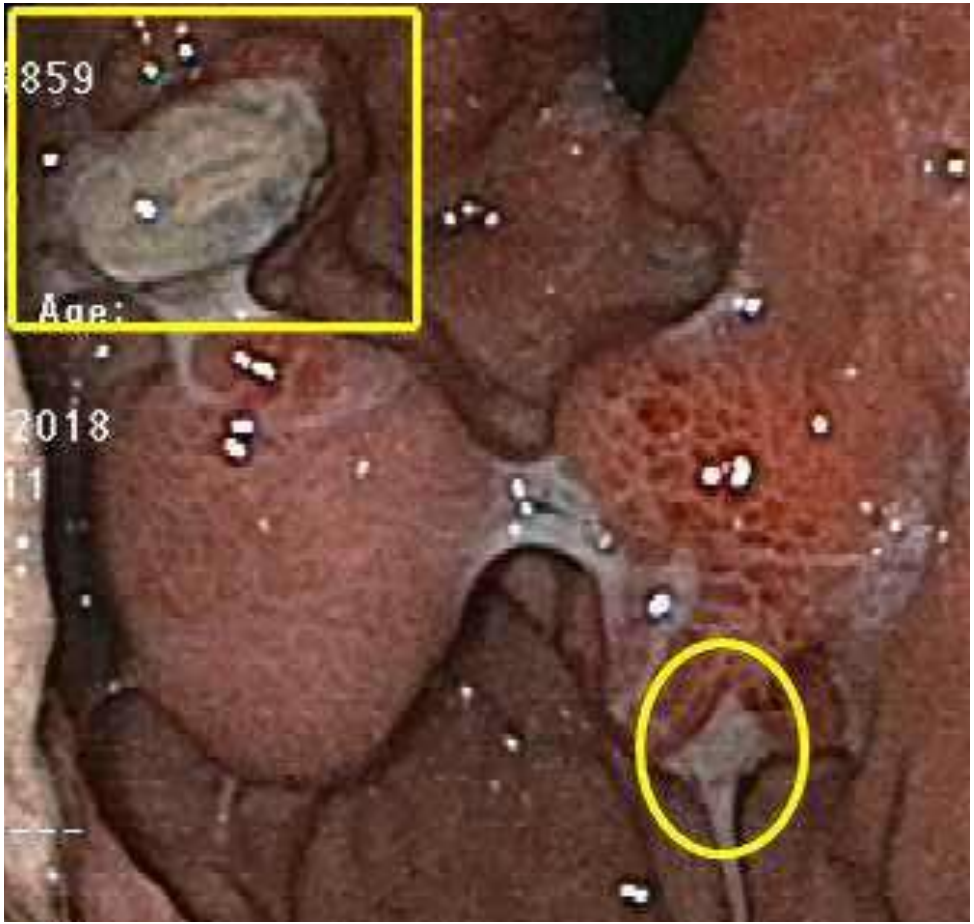


Case 1 - POD 34

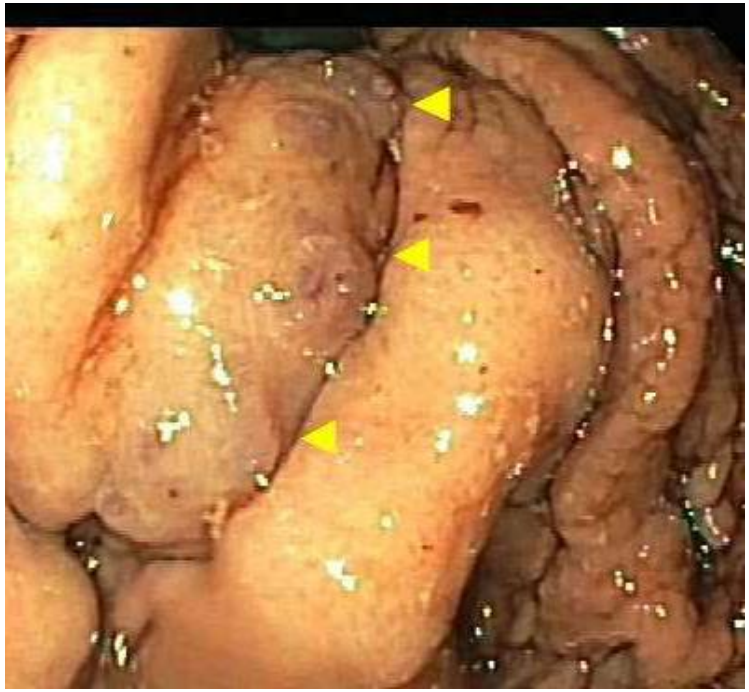


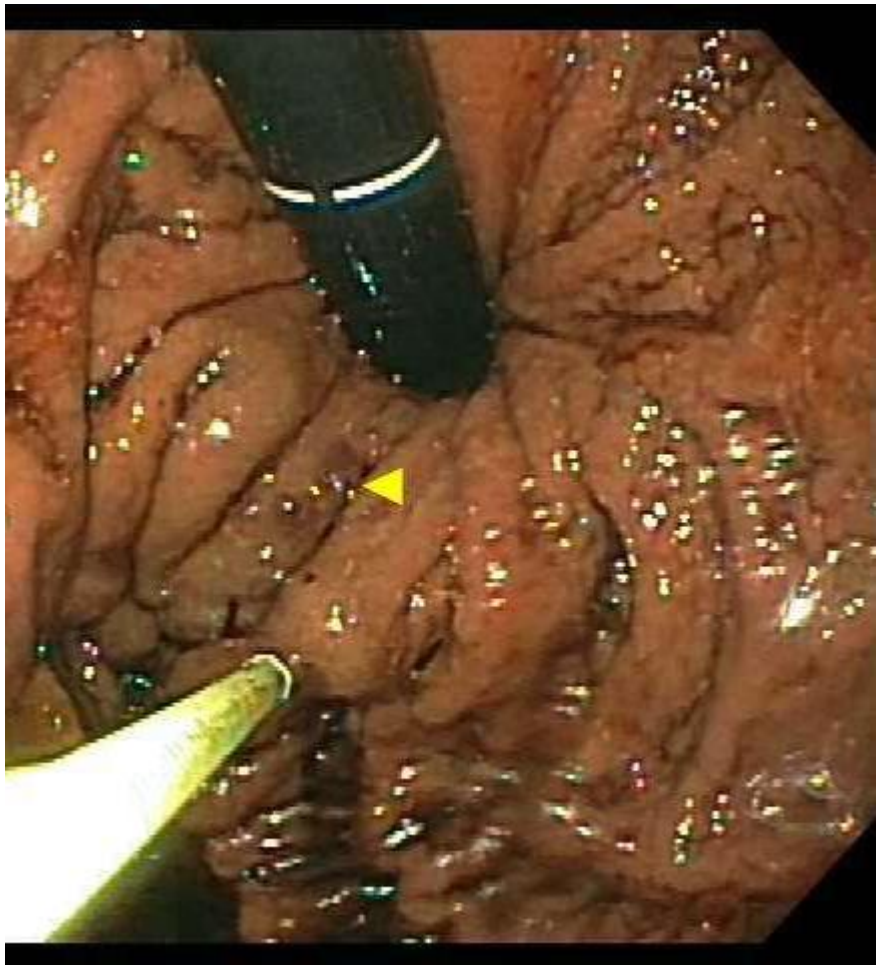


Case 1 – POD 110



Case 2

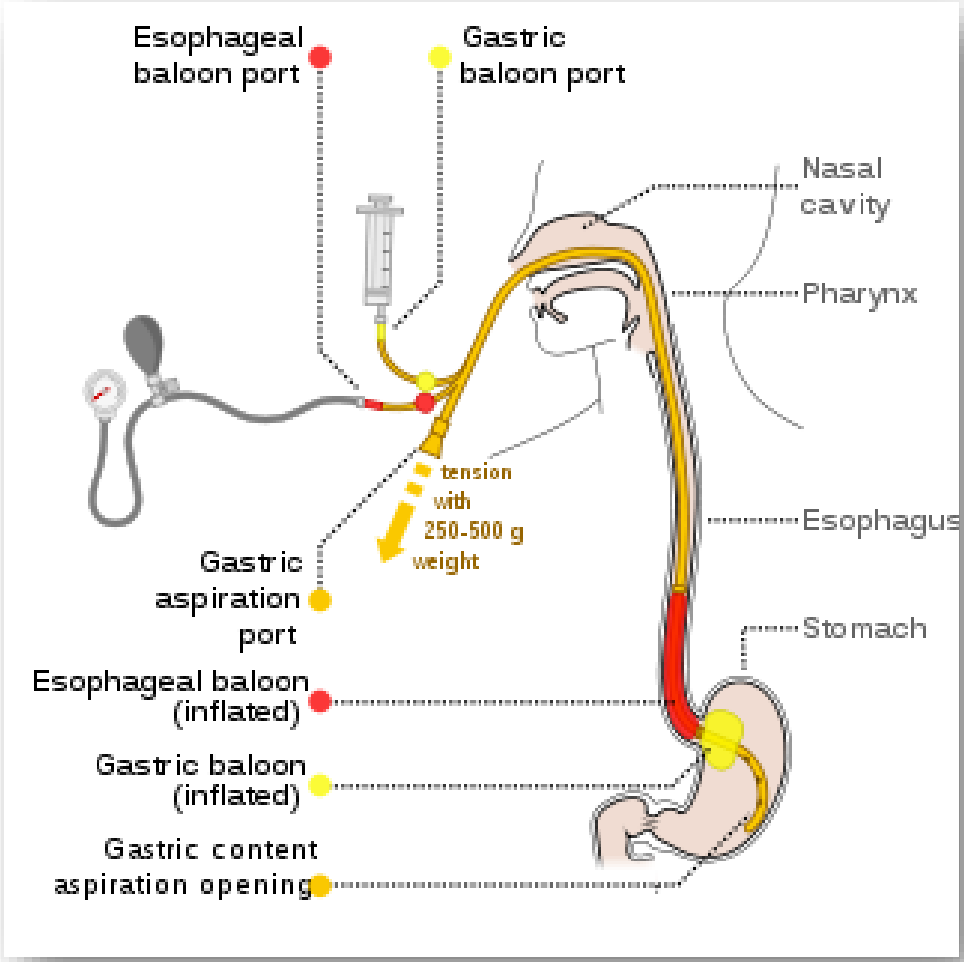




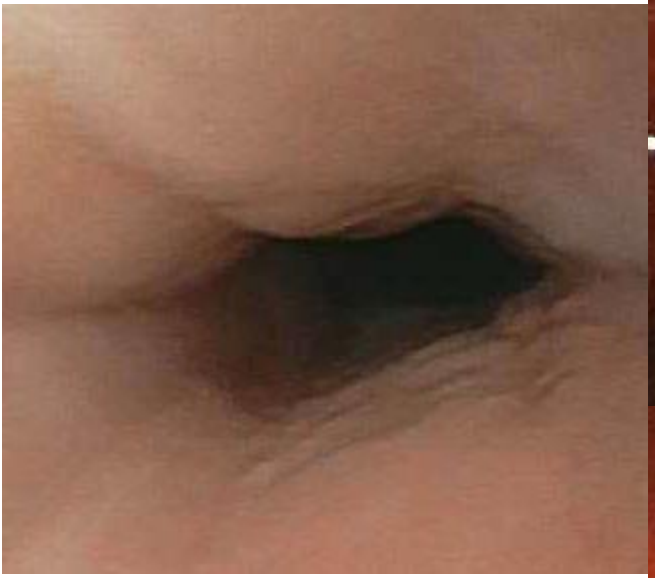
Treated with cyanoacrylate and then TIPS

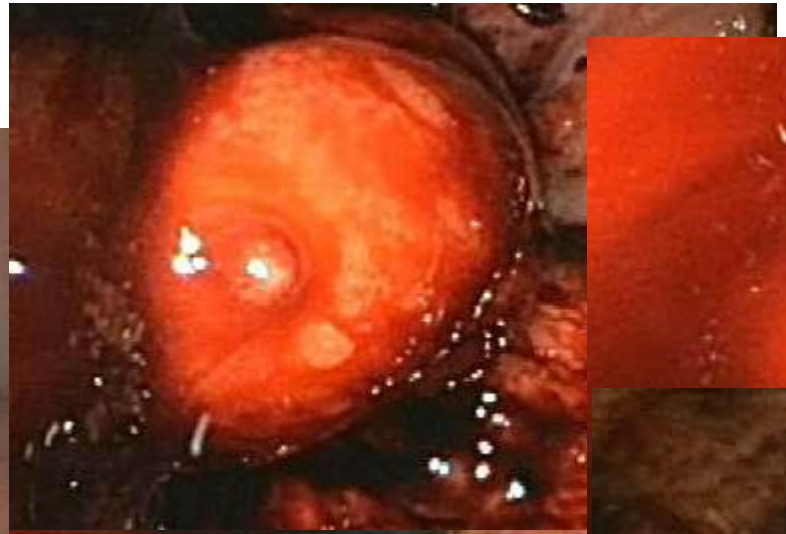
Sengstaken-Blakemore Tube

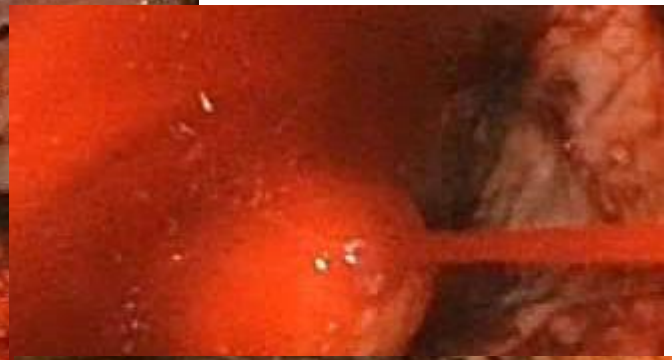
- Tamponade of life-threatening bleed due gastric or esophageal varices
- Only inflate gastric balloon

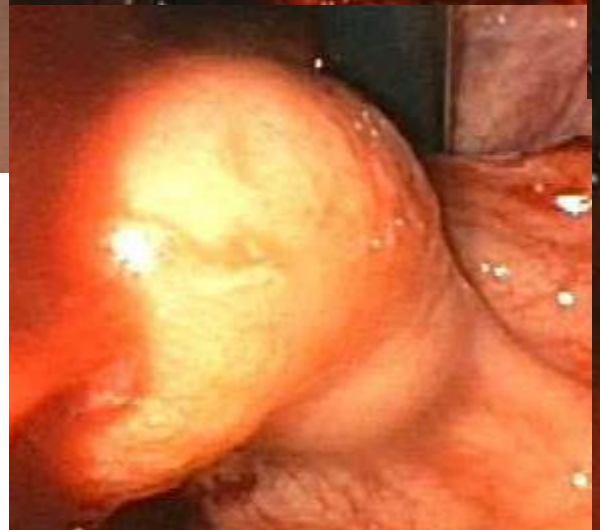


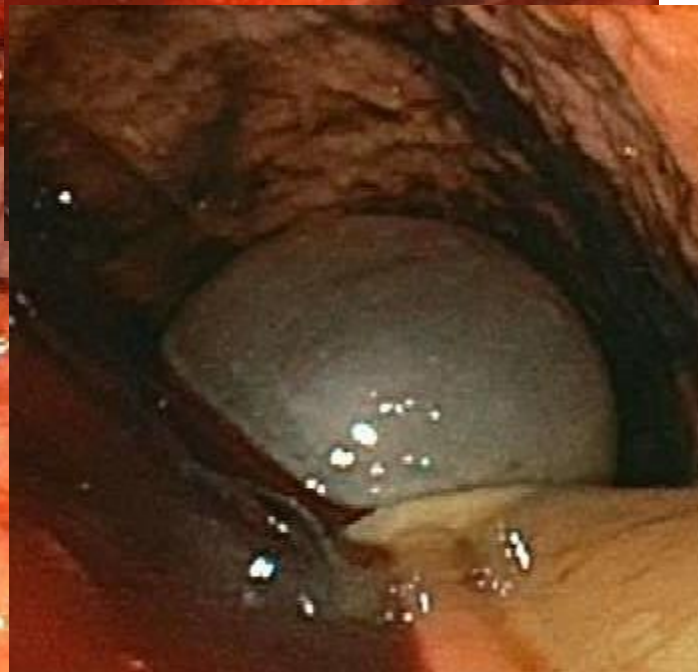
Case 3







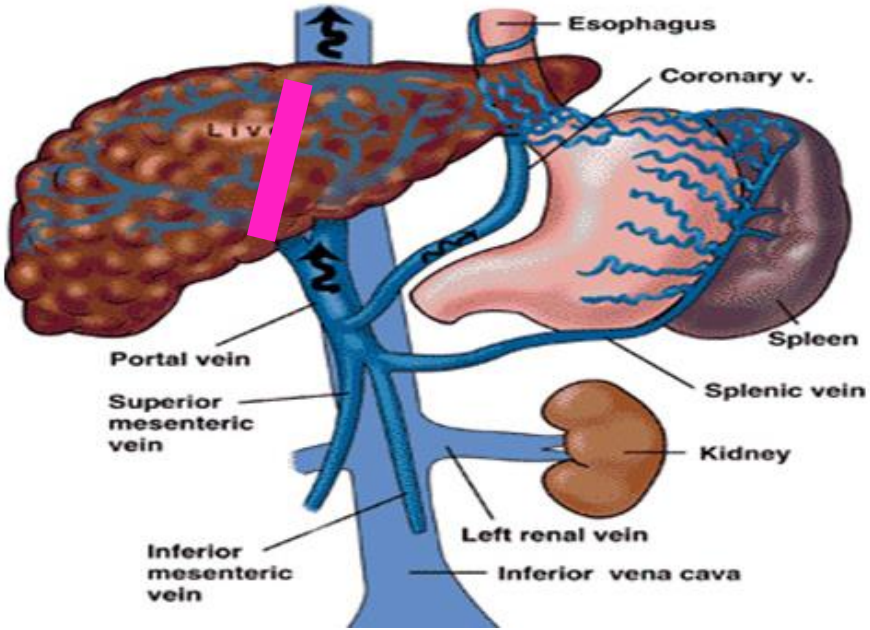


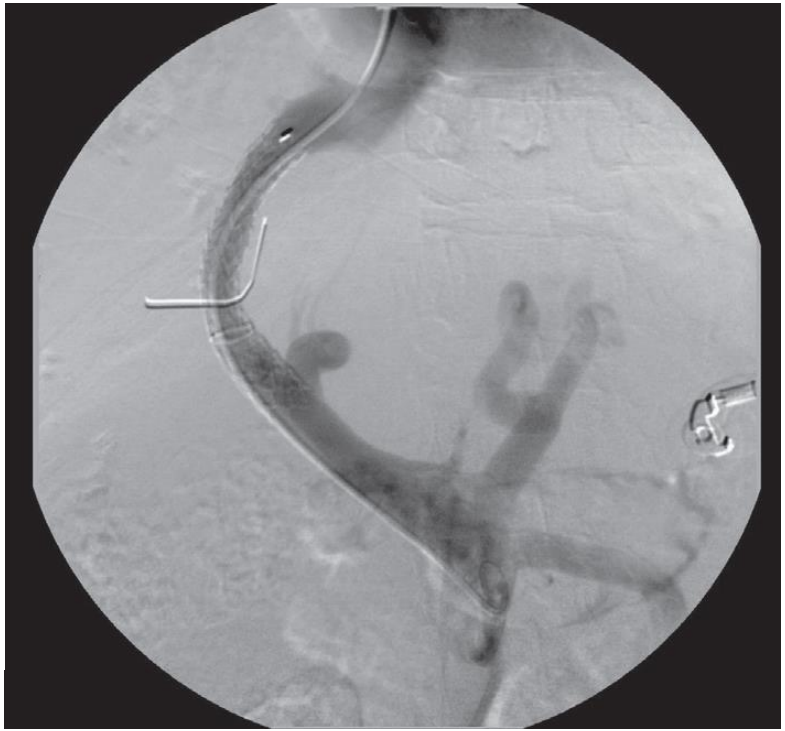


Prior history: Perforated diverticulitis s/p Hartmans pouch; sigmoid colectomy with colostomy

Bleed stopped with BRTO

TIPS – optimal treatment for portal hypertensive bleeding

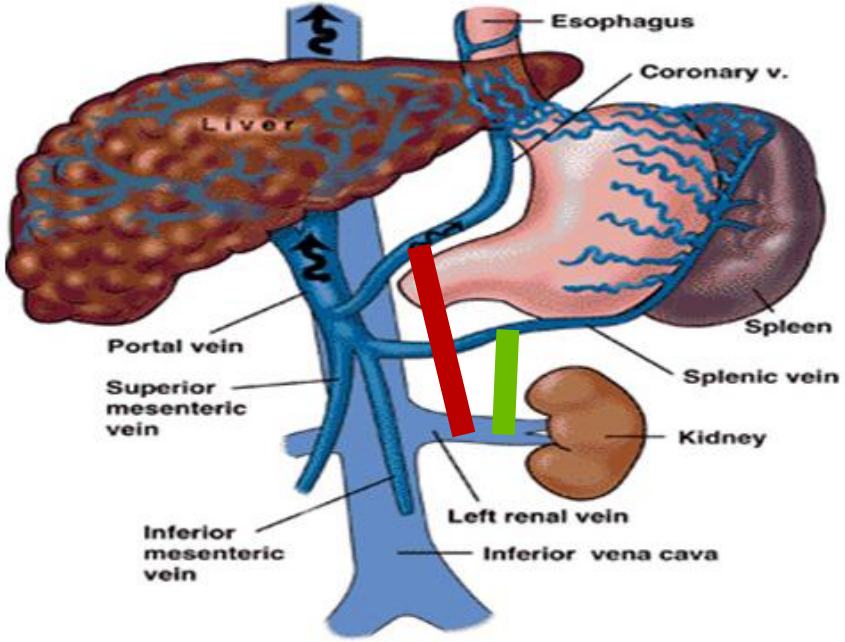




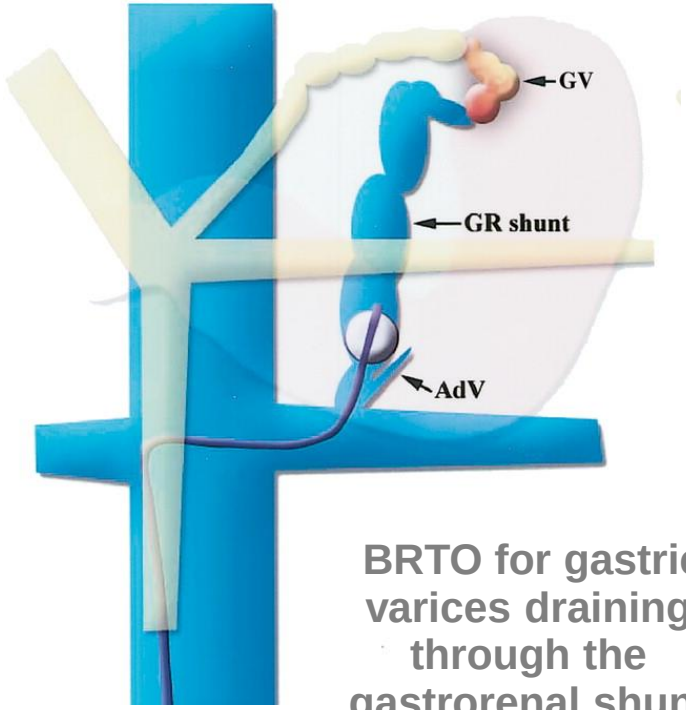
Rebleeding NNT: **2 patients**
Survival NNT: **4 patients**

Garcia-Pagan, et al. *New Eng J Med*; 2010; 362 (25):2370-2379
Lv Yong, et al. *The Lancet Gastroenterology & Hepatology* 2019: 4(8): 587-598

BRTO / BATO: Balloon-occluded Retrograde / Anterograde Transvenous Obliteration



Gastrorenal shunt; **Splenorenal shunt**



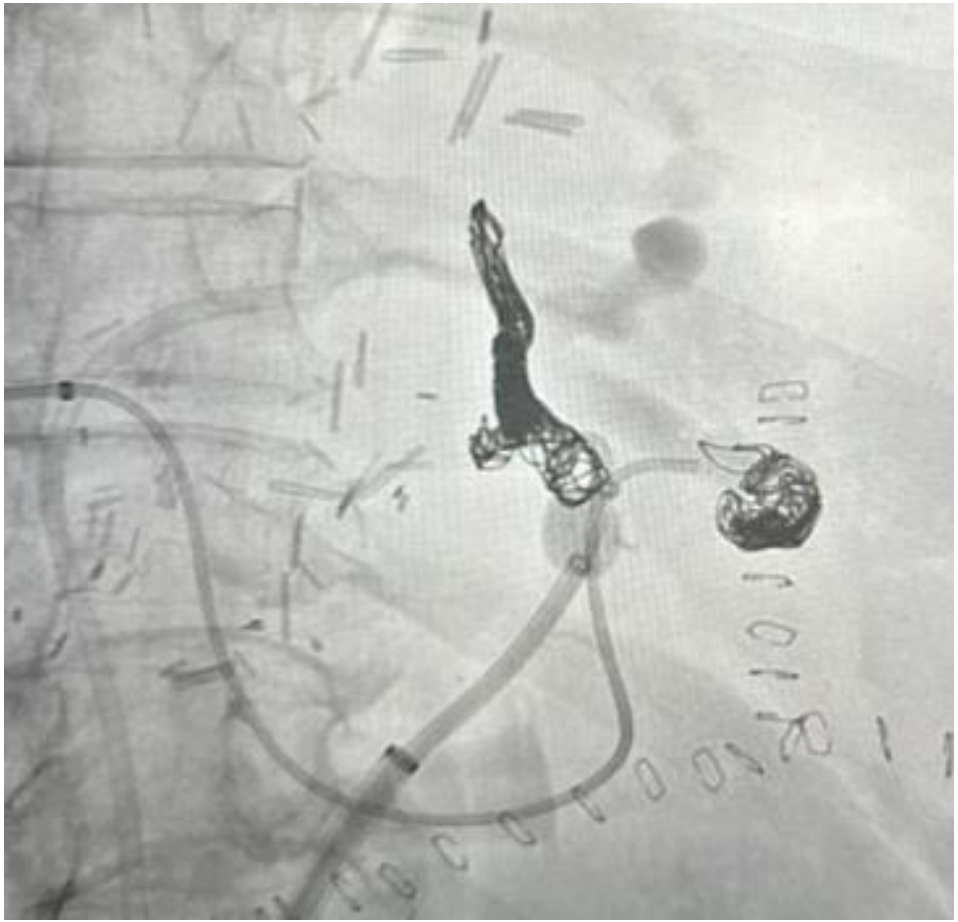
BRTO for gastric varices draining through the gastrorenal shunt

Case 4

Post-transplant patient with 3 life threatening upper GI bleeds; gastric varices noted on CTA

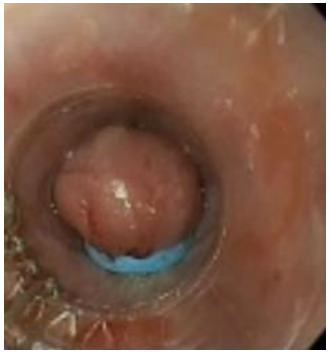
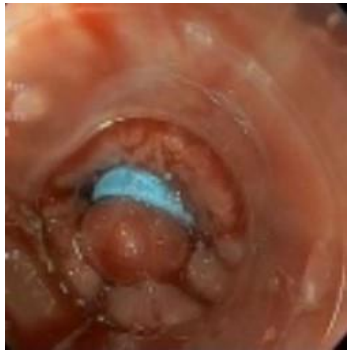
Cyanoacrylate injected on last EGD into varix on prior slide

Bleed stopped with BATO; No recurrence

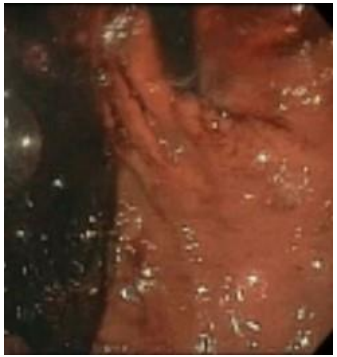
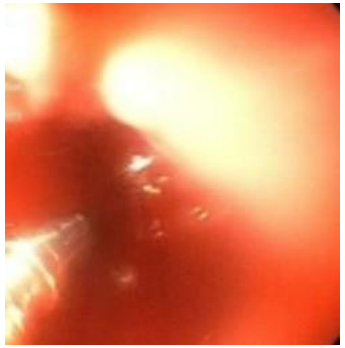
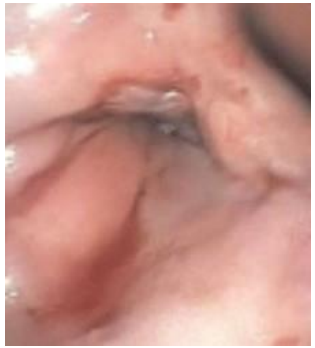


Case 5 Peri-Transplant Bleed

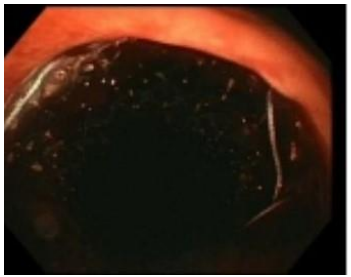
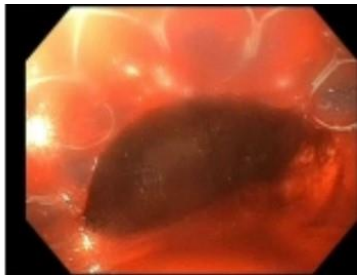
10 days pre-transplant – band ligation

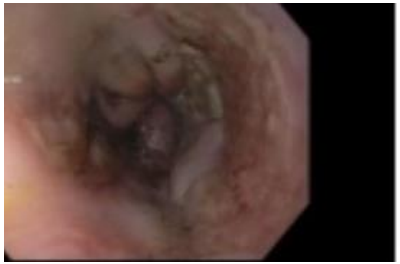
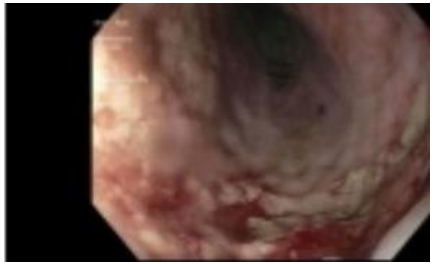
4 days pre-transplant – ethanolamine injection

During transplant – stent placement

3 weeks post-transplant – stent removal

McCarty TR and Njei B. *Digestive Endoscopy* 2016 Jul;28(5):539-47.

Alcoholic Cirrhosis Transplant Candidates

What is a Favorable Psychosocial Profile?

- First episode of severe alcoholic hepatitis / liver decompensating event
- Adequate sober social support
- Severe psychiatric disorders should be absent or treated
- Patients should have insight, agree with lifelong total abstinence and engagement in alcohol counseling
- Absent illicit substance abuse history
- Absence of alcohol-related legal issues
- Absence of failed rehab attempts

Alcoholic Cirrhosis Transplant Candidates

Sustained Alcohol Use Post-Liver Transplant
(SALT) Score

Variable	Points
>10 drinks/day at presentation	+4
≥2 prior failed rehabilitation attempts	+4
Any history of prior alcohol-related legal issues	+2
History of non-THC illicit substance abuse	+1

Score below 5 associated with a 95% negative predictive rate for sustained EtOH use post OLT

Lee, et al. Predicting Low Risk for Sustained Alcohol Use After Early Liver Transplant for Acute Alcoholic Hepatitis: The Sustained Alcohol Use Post-Liver Transplant Score. Hepatology.2019;69(4).

New Nomenclature

MASLD - Metabolic Dysfunction-Associated Steatotic Liver Disease in replacement of **NAFLD** (Non-Alcoholic Fatty Liver Disease)

MASH - Metabolic Dysfunction-Associated Steatohepatitis in replacement of **NASH** (Non-Alcoholic Steatohepatitis)

MetALD – MASLD and increased alcohol consumption

- 10 or more standard drinks for women (140 grams / week)
- 14 or more standard drinks for men (210 grams / week)

AASLD's Hepatology; ALEH's Annals of Hepatology, EASL's Journal of Hepatology, June 2023

How do GLP-1 Receptor Agonists Work?

The **–Glutides** [sema-, dula-, *lira-] and **Tirzepatide** [GLP-1 receptor angonist and glucose-dependent insulinotropic polypeptide (GIP) agonist]

Glucagon-like peptide-1 released from the small intestine after a meal

- Lowers serum glucose by inducing insulin secretion via incretin and reducing glucagon secretion
- Delays gastric emptying and suppresses appetite; quickly degraded
- Synthetic GLP-1 RAs are long acting with a 13 hour half life
- Improves glycemic control and aid in weight loss

Benefits of GLP1-RAs in MASLD

- A phase 2 randomized control trial studying semaglutide 2.4 mg vs placebo in patients with compensated NASH cirrhosis

  - Significant improvement in HgbA1c, body weight, and cholesterol
  - No hepatic decompensation or increased side effects in cirrhosis
  - AASLD recommends considering them in patients with obesity and diabetes given their potential benefit in MASLD
  - Weight loss of 5% reduces liver volume by 10%, decreases visceral adipose tissue mass by 10%, and decreases hepatic triglyceride content by 40%

Side Effects of GLP1-RAs

- Generally well tolerated
- May have nausea, vomiting and diarrhea
- Most side effects are dose dependent, can be transient
- Increased risk of cholelithiasis, may relate to rapid weight loss
- Increased rates of pancreatitis or pancreatic cancer were not seen in meta-analysis
- Contraindicated in patients with a history of pancreatitis, multiple endocrine neoplasia (MEN) 2A, MEN 2B, and medullary thyroid carcinoma

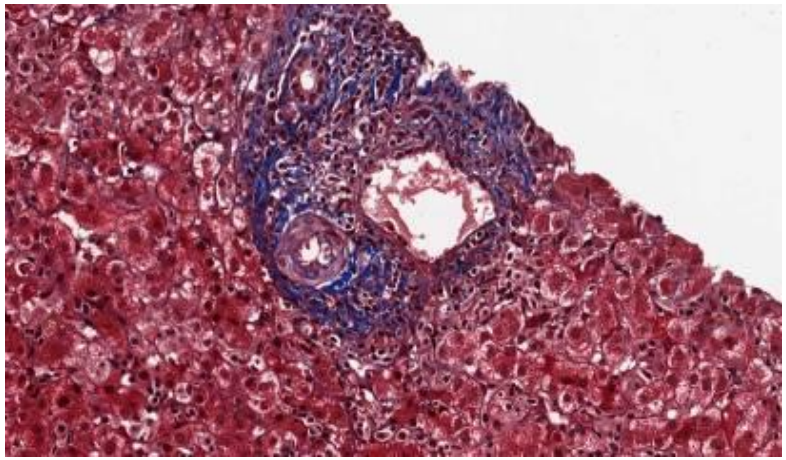
Resmetirom

Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. S.A. Harrison, et al. *NEJM* 2024;390:497-509.

- Oral, liver-directed, thyroid hormone receptor beta–selective agonist for treating MASH with hepatic fibrosis.
- Biopsy-confirmed MASH and fibrosis stage of F1B, F2, or F3 (range from F0 [no fibrosis] to F4 [cirrhosis]). Patients randomly assigned in a 1:1:1 ratio to receive once-daily resmetirom at a dose of 80 mg or 100 mg or placebo.
- **Two primary end points** at week 52
  - NASH resolution (reduction of MASLD activity score by 2 or more points; scores range from 0 to 8) with no worsening of fibrosis
  - Improvement (reduction) in fibrosis by at least one stage with no worsening of the NAFLD activity score.

Histology – Staging Hepatic Fibrosis (F0-4)

1



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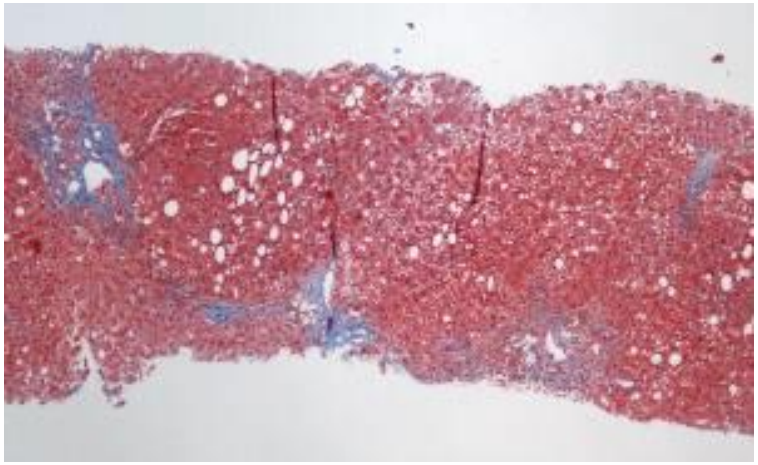

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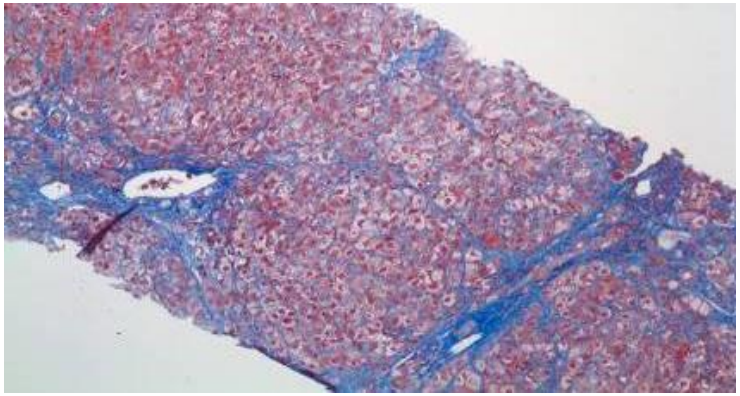

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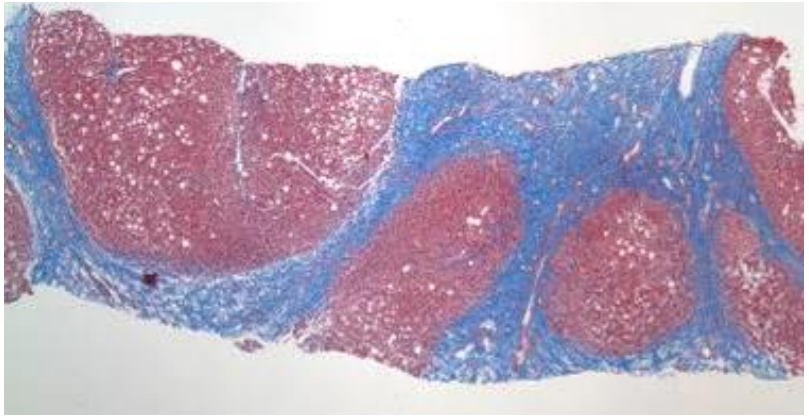
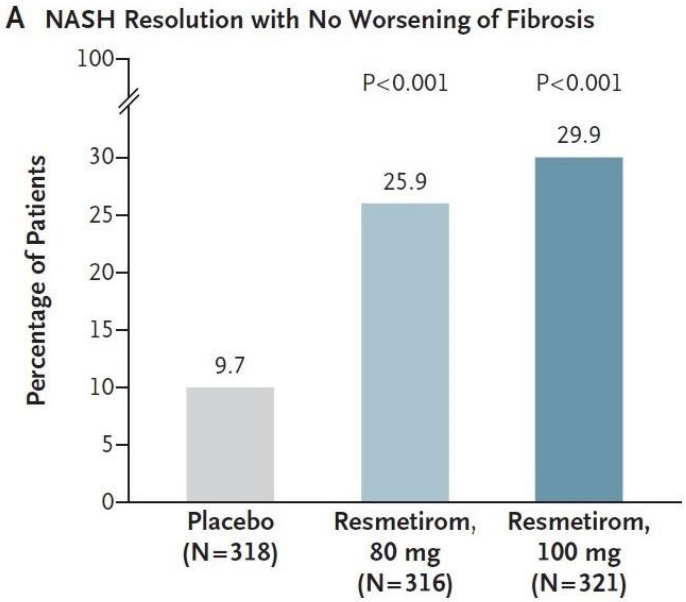


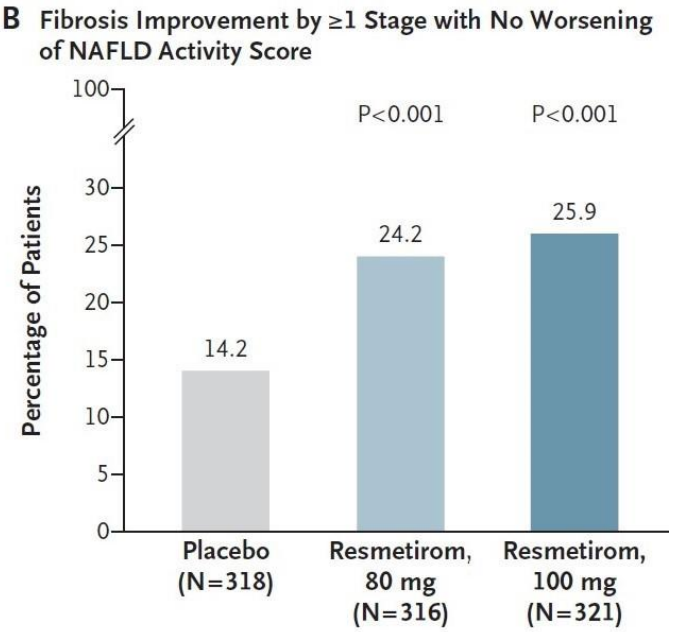
Resmetirom

FDA Approved

Significant LDL improvement at 24 weeks

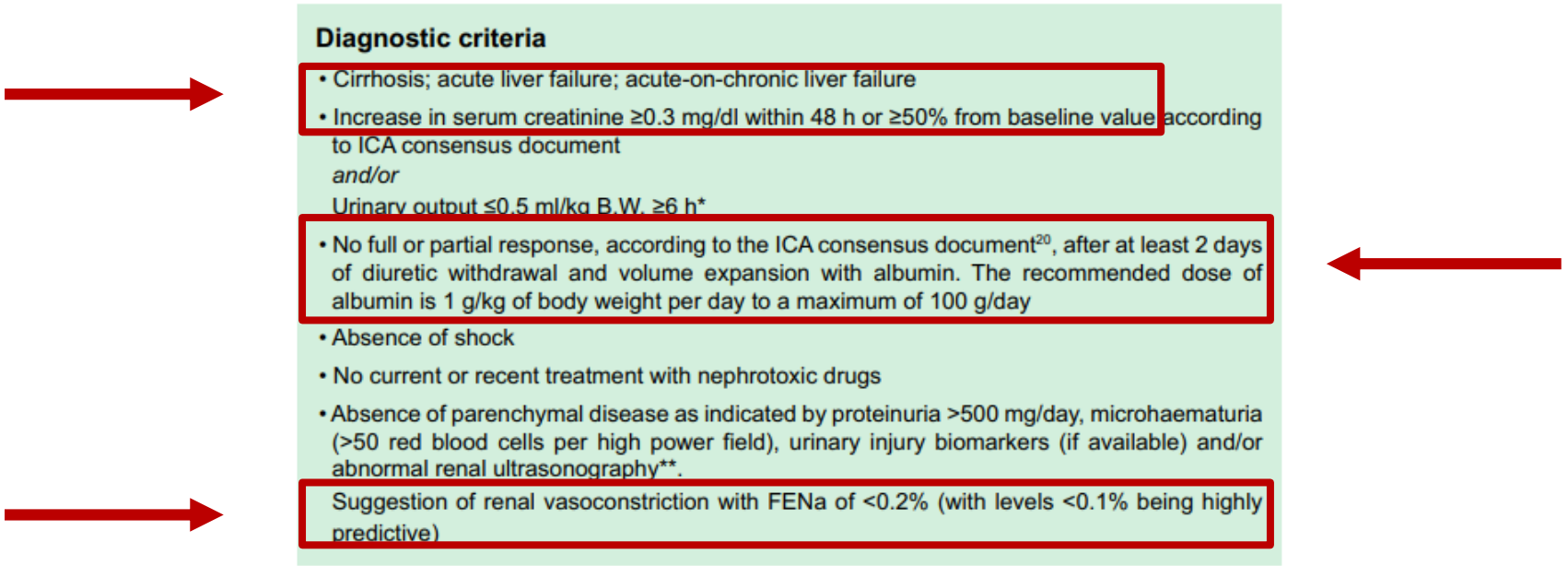
Side effects: diarrhea and nausea





Both the 80-mg dose and the 100-mg dose of resmetirom were superior to placebo with respect to NASH resolution and improvement in liver fibrosis by at least one stage.

What is Hepatorenal Syndrome?



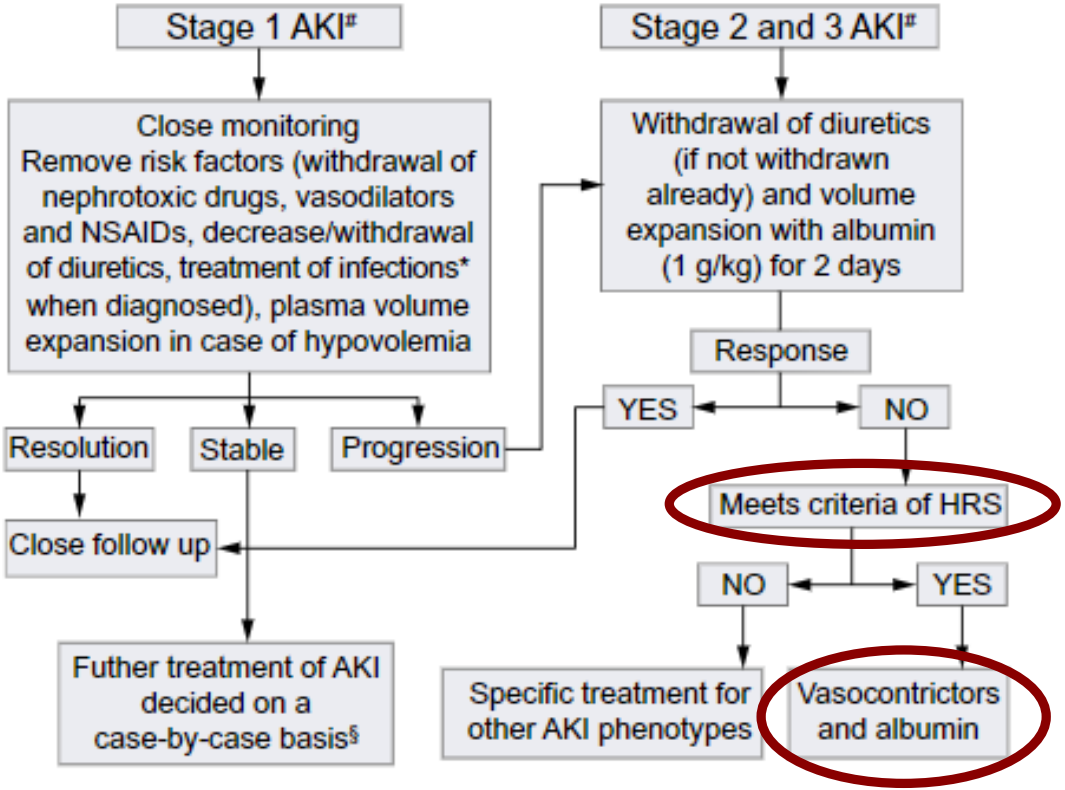
Diagnostic criteria

- Cirrhosis; acute liver failure; acute-on-chronic liver failure
- Increase in serum creatinine ≥0.3 mg/dl within 48 h or ≥50% from baseline value according to ICA consensus document
  and/or
  Urinary output ≤0.5 ml/kg B.W. ≥6 h*
- No full or partial response, according to the ICA consensus document[20], after at least 2 days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day to a maximum of 100 g/day
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal disease as indicated by proteinuria >500 mg/day, microhaematuria (>50 red blood cells per high power field), urinary injury biomarkers (if available) and/or abnormal renal ultrasonography**.
- Suggestion of renal vasoconstriction with FENa of <0.2% (with levels <0.1% being highly predictive)

*The evaluation of this parameter requires a urinary catheter. **This criterion would not be included in cases of known pre-existing structural chronic kidney disease (*e.g.* diabetic or hypertensive nephropathy). AKI, acute kidney injury; FENa, fractional excretion of sodium; HRS, hepatorenal syndrome; ICA, International Club of Ascites.

Angeli P, et al. New in pathophysiology, definition and classification of hepatorenal syndrome: A step beyond the International Club of Ascites (ICA) consensus document. Journal of Hepatology 2019;71:811-822.

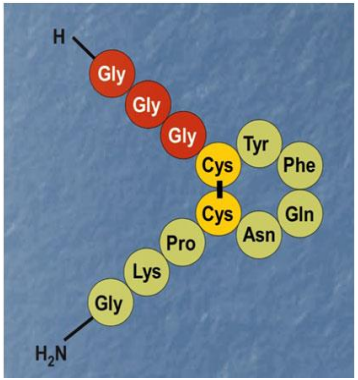
Algorithm for AKI Management in Cirrhosis

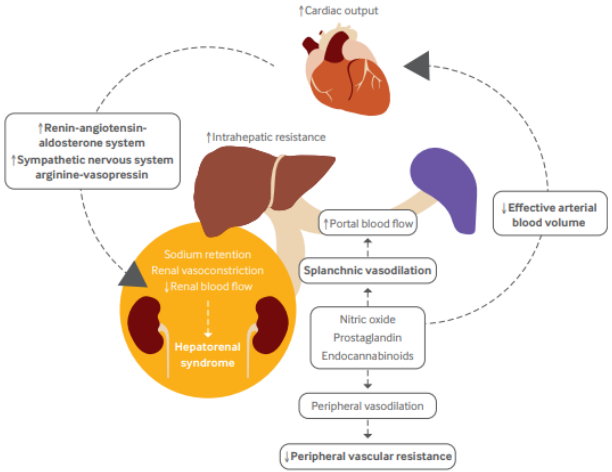


Angeli P, et al. Diagnosis and Management of Acute Kidney Injury in Patients with Cirrhosis: Revised consensus recommendations of the International Club of Ascites. J Hepatology 2015;62: 968-74

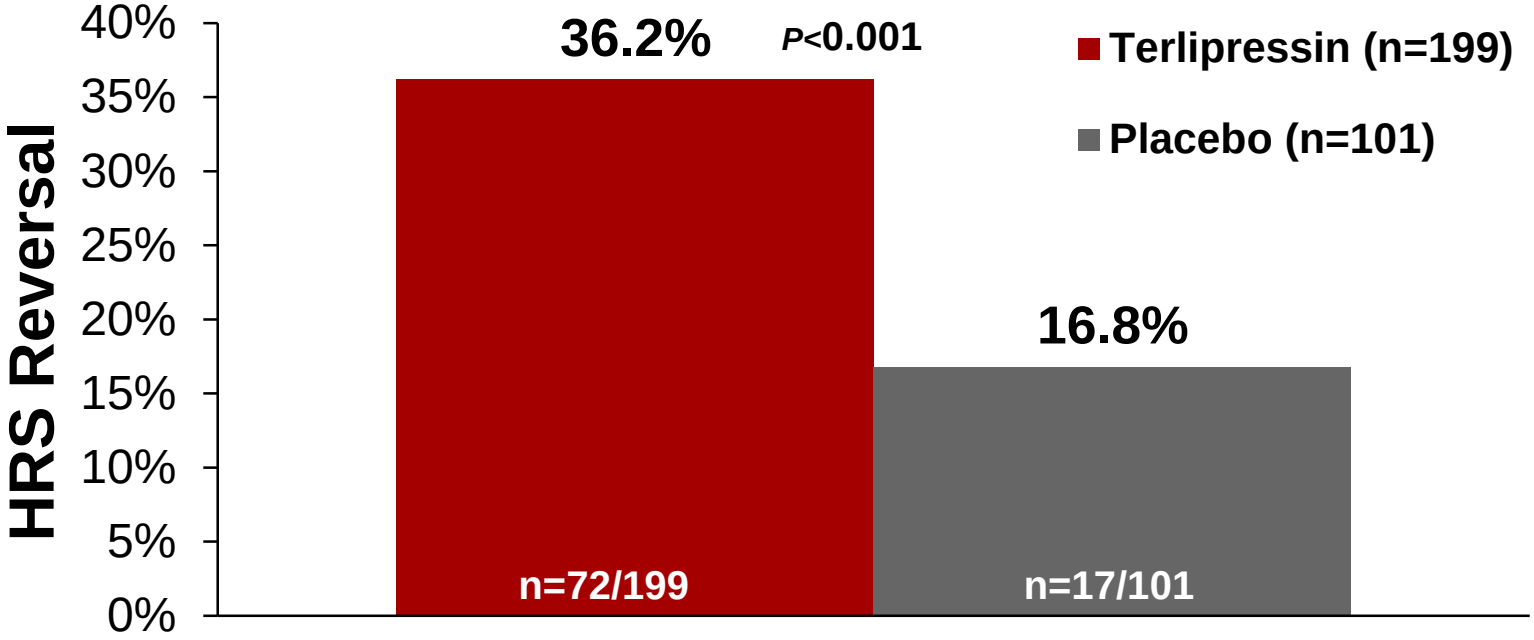
Terlipressin

- A synthetic vasopressin analogue
- Greater affinity for V_1 receptors located in the smooth muscle cells of splanchnic vasculature
- Reduces splanchnic blood inflow and therefore portal pressure
- Redistributes part of the intravascular volume to the central circulation
- Evidence that Terlipressin improves renal function in patients with HRS-1
- Drug of choice for HRS wherever available





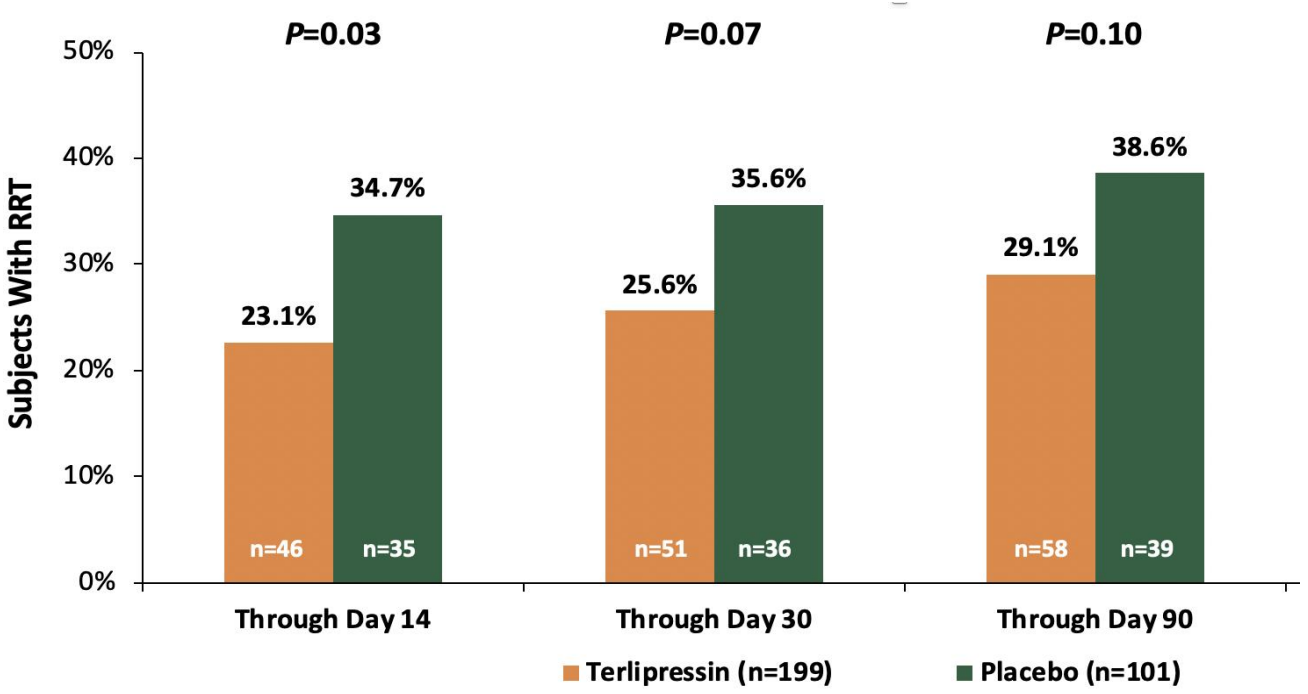
The CONFIRM Study: HRS Reversal (HRSR)



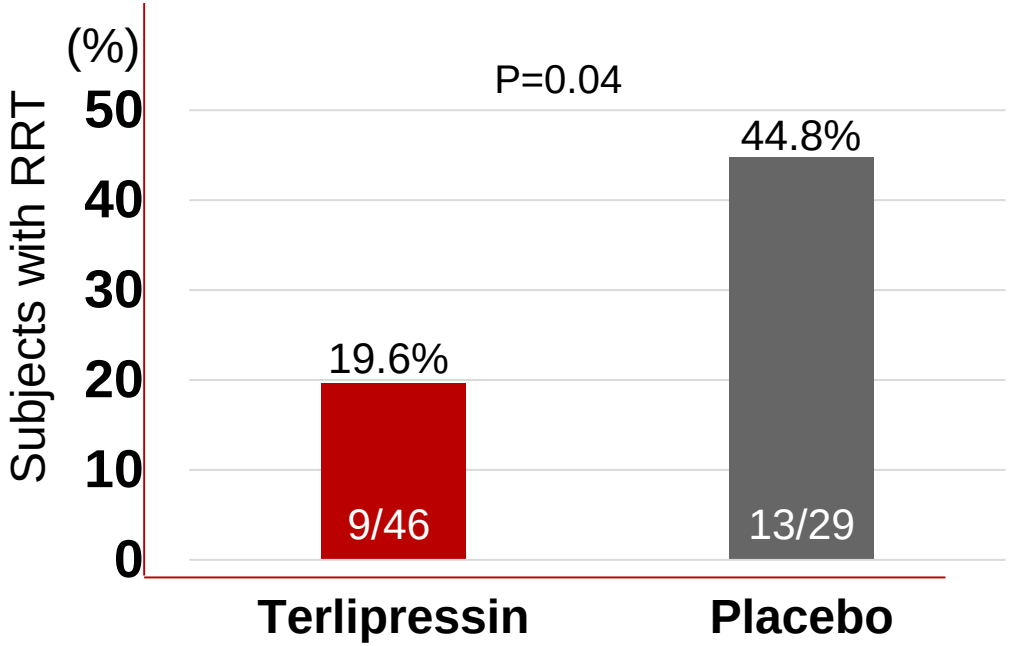
The incidence of HRS reversal is defined as the %age of subjects with SCr value ≤1.5 mg/dL while on treatment by Day 14 or discharge.

***SCr values after renal replacement therapy, transjugular intrahepatic portosystemic shunt, liver transplant, or open-label vasopressor use are excluded.**

The CONFIRM Study: Percentage of Patients needing RRT Through Day 90



The CONFIRM Study: Percentage of Patients needing RRT Post–Liver Transplant



Brief Example Case

Acute on chronic liver failure with multi-system organ failure (kidney, sepsis, coagulopathy) and severe AKI (Creatinine over 5)

- **Is this HRS-AKI?**
  - Not sure; hold diuretics, albumin 25%, Antibiotics for SBP
- **Are you going to start Terlipressin?**
  - Not indicated due to presence of ACLF-3.
  - Low response rate to Terlipressin when Creatinine > 5
- **Any role of Octreotide + Midodrine (HRS cocktail)**
  - **No role at all. Not effective for HRS-AKI in multiple RCT**

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