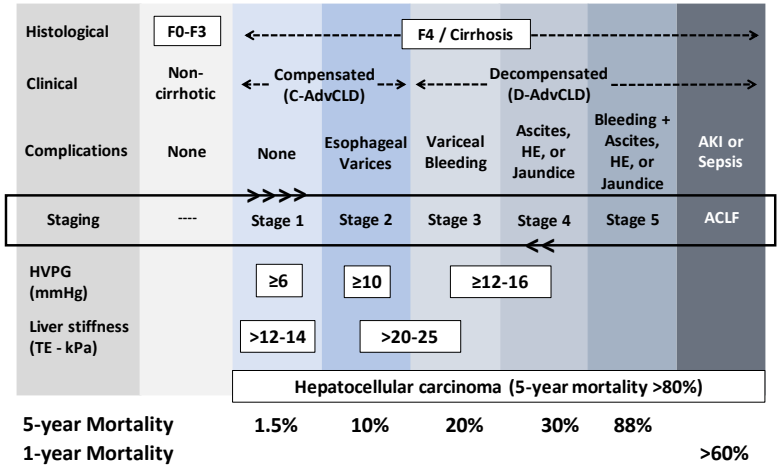
What is new in the management of cirrhosis?

Andrés Duarte-Rojo
Medical Director of Liver Transplantation

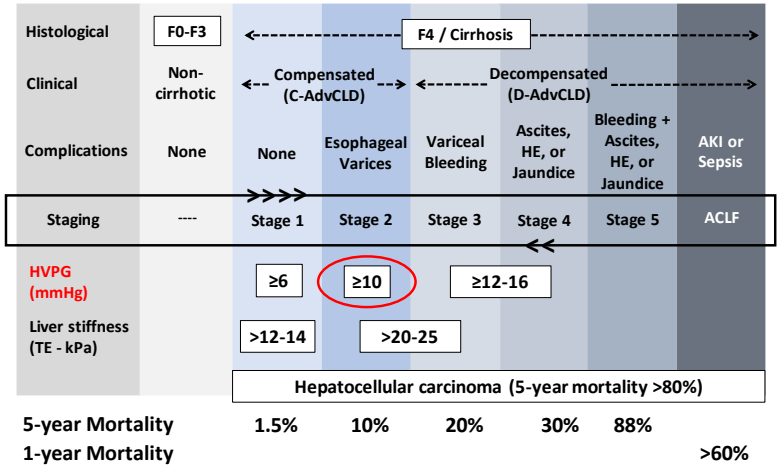
2020 Annual Update in Medical Hepatology

December 5th, 2020

Objectives

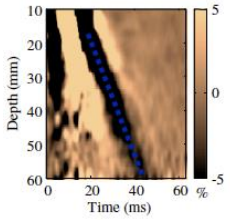


Objectives



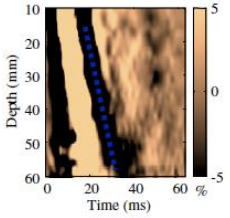
Clinically significant portal hypertension (CSPH)

- Marks the transition from low to high risk of decompensation / death
  - Traditionally identified through hepatic venous pressure gradient (HVPG) ≥10 mmHg



VCTE-LSM of 12 kPa

10-15 kPa (13.6) rules out CSPH with sensitivity >90%



VCTE-LSM of 27 kPa

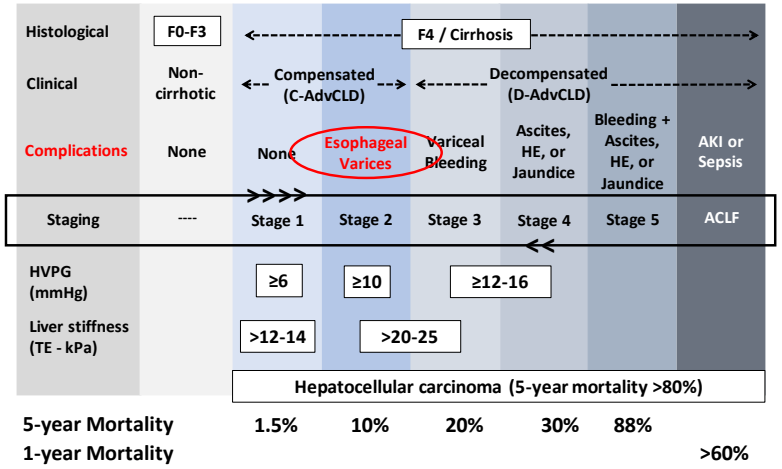
20-25 kPa (21) rules in CSPH with specificity >90%

Two societies have endorsed (AGA, Baveno) elastography to identify CSPG

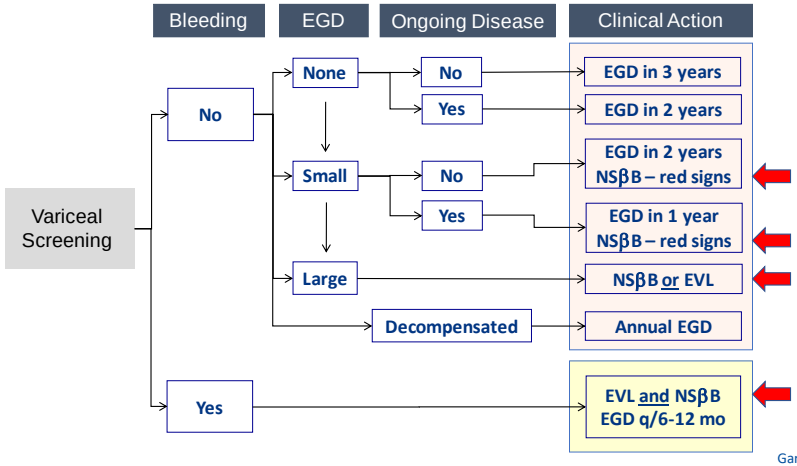
AASLD expected to release the Non-Invasive Liver Disease Assessment (NILDA) Practice Guidance in 2021

Mandorfer. Semin Liver Dis 2020;40:240

Objectives



Prophylaxis of variceal bleeding



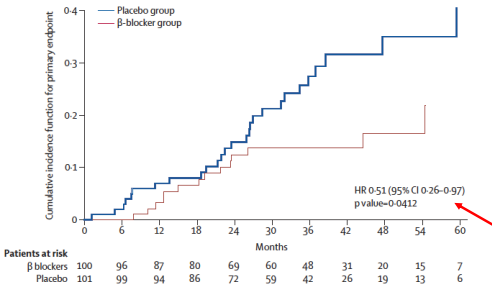
Garcia-Tsao. Hepatology 2016;65:310
de Franchis. J Hepatol 2015;63:743

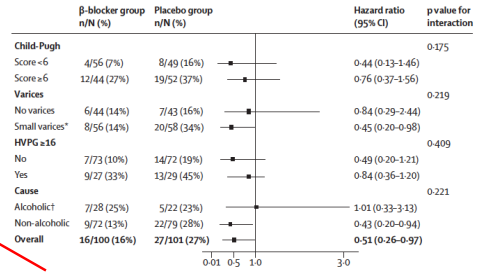
Other benefits of beta-blockers

- Can beta blockers help prevent decompensation and death?
  - 201 patients: all with HVPG ≥10 mmHg and NSBB acute response in 66%

Responders = propranolol ≤160 mg/d vs. pbo

Non-responders = carvedilol ≤25 mg/d vs. pbo



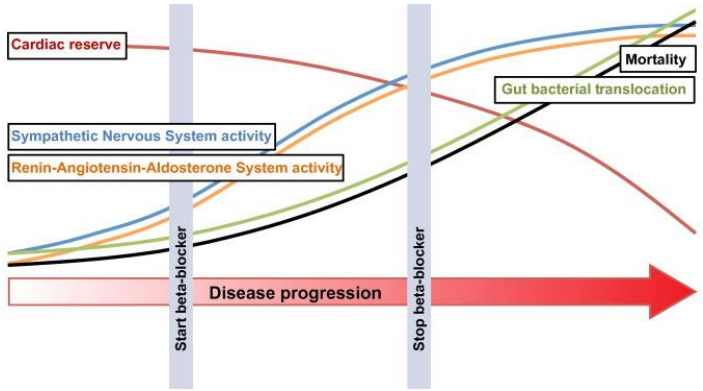


Driven by ascites!

Villanueva. Lancet 2019;393:1597

Beta-blockade therapeutic window

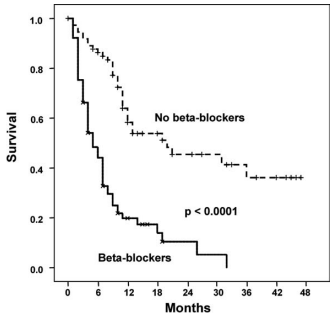
- When should we stop beta-blockers?



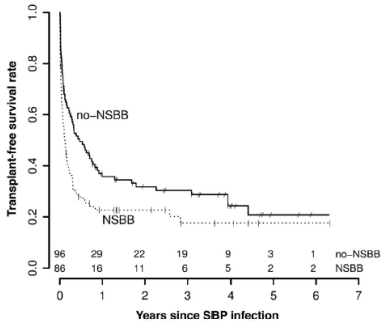
Ge. J Hepatol 2014;60:643

Beta-blockade therapeutic window

- Negative effects of beta blockers



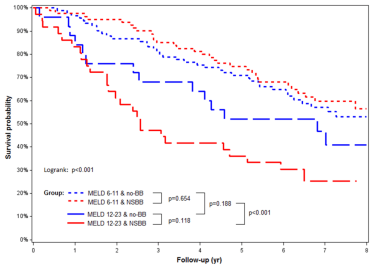
Sertse. Hepatology 2010;52:1007

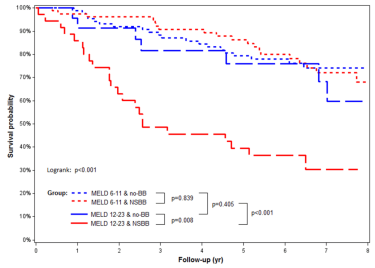


Mandorfer. Gastroenterology 2014;146:1680

Beta-blockade therapeutic window

- Negative effects of beta blockers
  - Increased mortality in alcohol-related cirrhosis if MELD ≥12

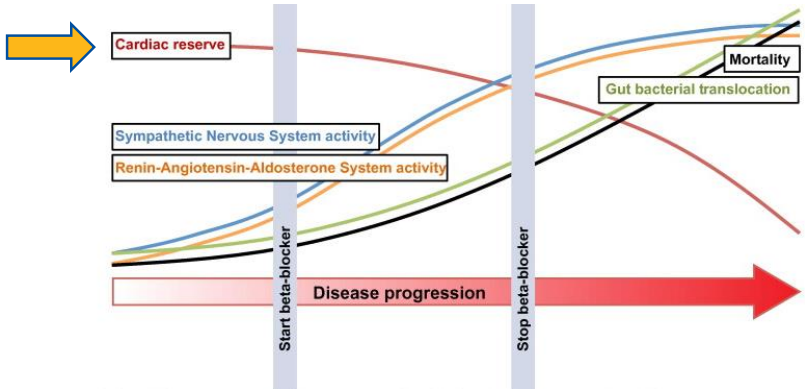




Cales. Liver Int 2020;in press
Facciorusso. Dig Dis Sci 2018;63:1737
Onali. Liver Int 2017;37:1334
Scheiner. Scand J Gastroenterol 2017;52:1008

Beta-blockade therapeutic window

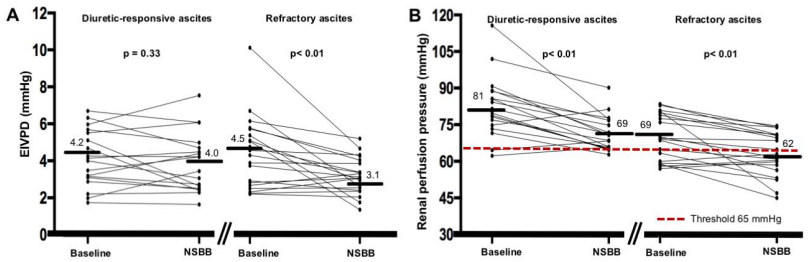
- When should we stop beta-blockers?



Ge. J Hepatol 2014;60:643

Beta-blockade therapeutic window

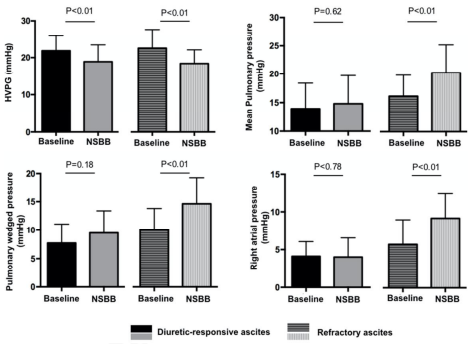
- Beta blockers affects cardiac systolic function and renal perfusion pressure
  - Diuretic-responsive ascites (n=18) vs. refractory ascites (n=20) after 4 weeks of NSBB



Tellez. J Hepatol 2020;73:1404
Thomas. Circulation 2005;112:1684

Beta-blockade therapeutic window

- Beta blockers affects cardiac systolic function and renal perfusion pressure
  - Diuretic-responsive ascites (n=18) vs. refractory ascites (n=20) after 4 weeks of NSBB



Apart from dropping HVPG (as expected), NSBB increased…

- Pulmonary wedged pressure (PCWP)
- Pulmonary pressure (mPAP)
- Right atrial pressure

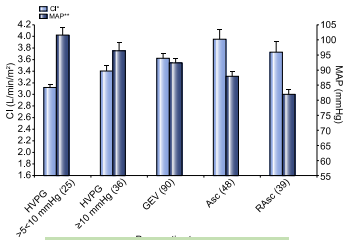
…only in those with refractory ascites

Translated: NSBB worsened hyperdynamic circulation of cirrhosis

Tellez. J Hepatol 2020;73:1404

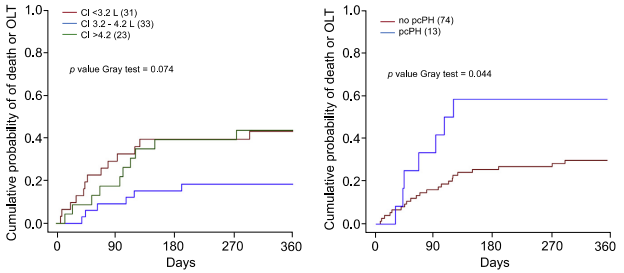
Beta-blockade therapeutic window

- Cardiopulmonary hemodynamics and worse clinical outcomes in cirrhosis
  - 238 patients with "per protocol" catheterization



Progressive liver disease: MAP↓ while CI ↑

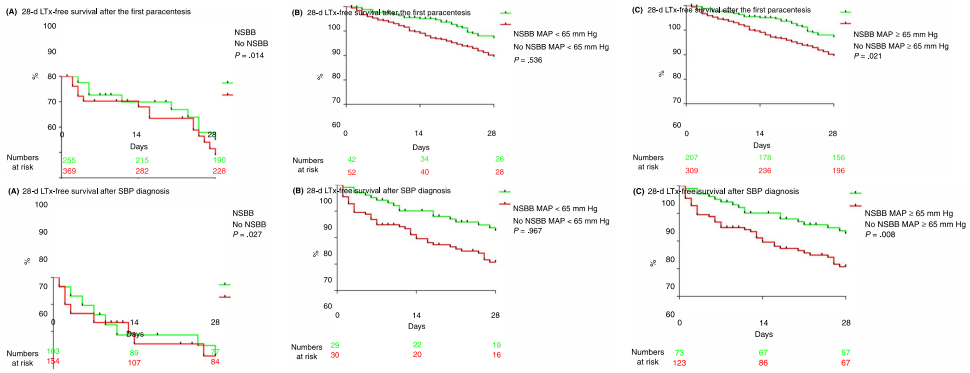
Hyperdynamic circulation (CI) and mPAP + PCWP predict mortality or LT



Turcot. J Hepatol 2018;73:1404

Beta-blockade therapeutic window

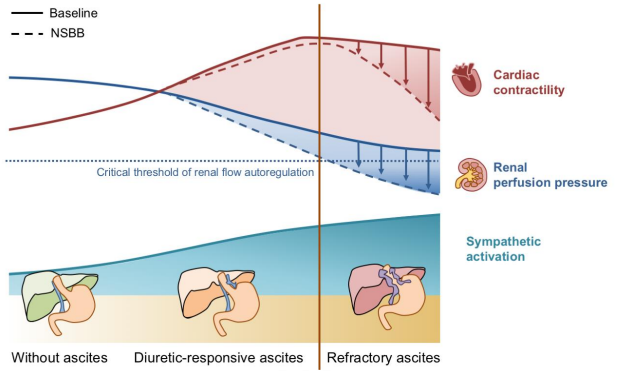
- Impact of beta blockers on survival following a hospital admission
  - Decompensated cirrhosis w/ascites (n=647), endpoint 28-day mortality



Tergast. Aliment Pharmacol Ther 2019;50:696

Beta-blockade therapeutic window

- When should we stop beta-blockers?

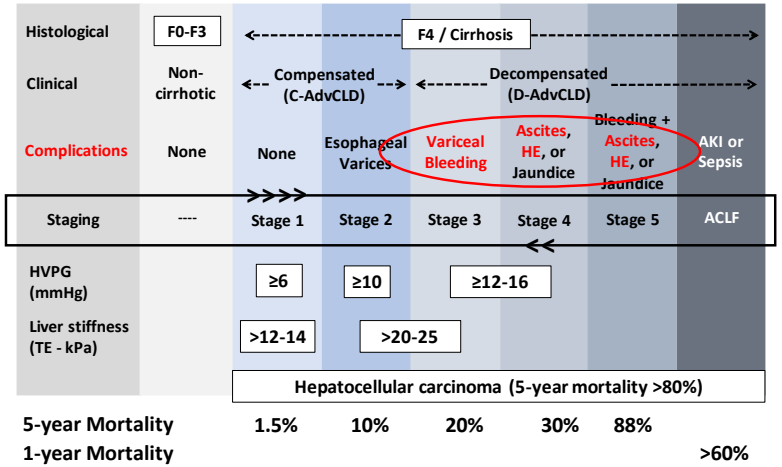


When the balance between sympathetic activation and cardiac function is broken and affect autoregulation

Perhaps…
- Refractory ascites and SBP with high MELD
- When MAP <65 mmHg
- The frail?

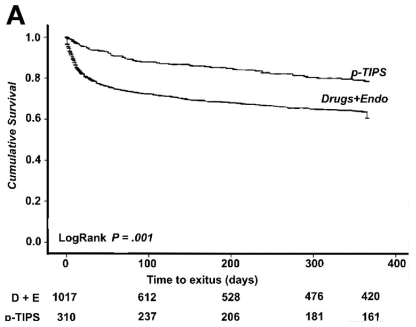
Tellez. J Hepatol 2020;73:1404

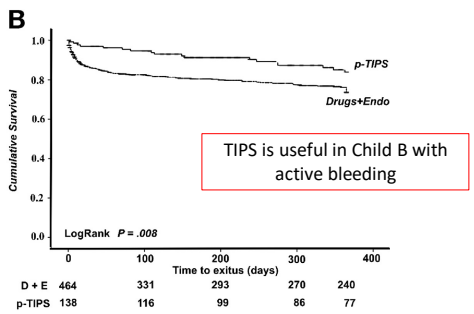
Objectives



Preemptive TIPS - acute variceal bleeding

- 1-year mortality for TIPS within 72 hrs vs. EGD EBL + NSBB in CTP <14
  - CTP B + active bleeding and CTP B – meta-analysis of 7 studies with 1327 patients





TIPS is useful in Child B with active bleeding

Nicoara-Farcau. Gastroenterology;in press
Hernandez-Gea. Hepatology 2019;69:282

Post-TIPS HE

- Develops in 20-50% of cases and it is refractory in ≈10%

Risk Factors	Adjusted Hazards Ratio
Age	**1.05 (1.02–1.08)**
Prior OHE Minimal HE	**2.45 (1.66–3.58)** 1.79 (1.21–2.65)
CTP B **CTP C**	**2.57 (0.61–10.8)** **4.32 (0.96–19.3)**
Bilirubin (each 0.6 ↑)	1.06 (1.03–1.08)
Creatinine (each 0.1 ↑)	1.09 (1.05–1.13)
Albumin (each 0.5 ↓)	0.68 (0.56–0.83)
Sodium (each 5 ↑)	0.63 (0.53–0.74)
Portocaval gradient (1 mmHg ↓)	**1.16 (OR)**
Diabetes	1.86 (1.20–2.87)
Other	Sarcopenia, PPI, NSBB, statin

Only if desperate with a MELD >20

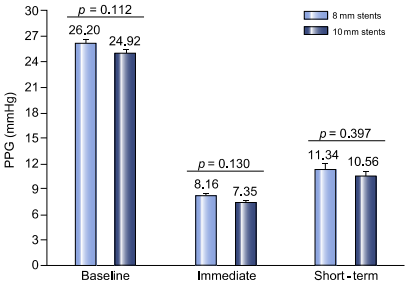
Probably not a good idea if MELD >15

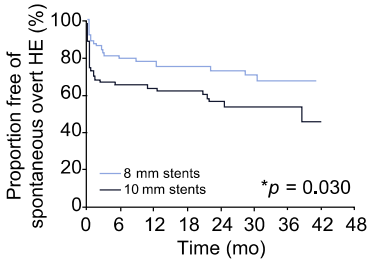
Be certain about proper indication for TIPS

Schindler. J Clin Med 2020;9:3784

Post-TIPS HE

- Smaller diameter TIPS are safer (without compromising efficacy)
  - 127 patients randomized to 8 vs. 10 mm stents

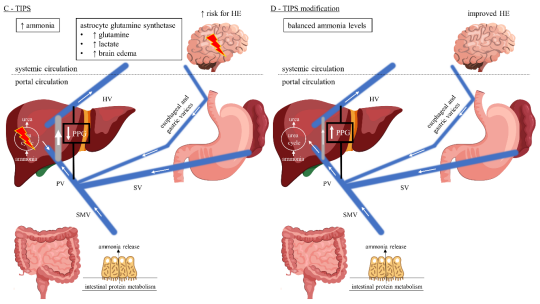




Wang. J Hepatol 2017;67:508

Post-TIPS HE

- Treatment of refractory HE

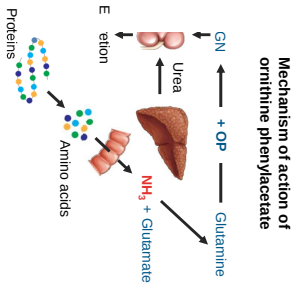


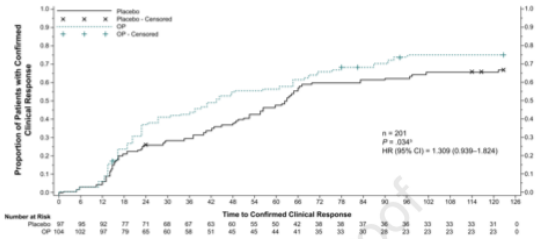
No. with Refractory HE/Treated with TIPS	Child–Pugh Class	No. of Patients Improved	PPG Pre (mmHg)	PPG Post (mmHg)
3/82	B: 1 C: 2	3	5.6 ± 3.2	12.1 ± 2.7
2/38	B: 1 C: 1	2	6.5 ± 2.6	12.7 ± 3.8
1/29	C: 1	1	-	-
10/174	-	8	8.6 ± 4.1	13.0 ± 4.0
20/344	A: 7 B: 9 C: 4	11	7.7 ± 3.9	12.1 ± 4.4

Schindler. J Clin Med 2020;9:3784

Post-TIPS HE

- Ornithine phenylacetate (OPA)



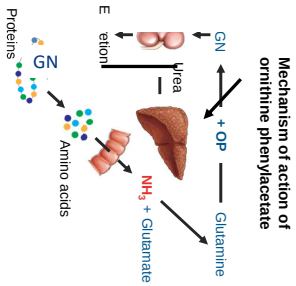


21 h ↓ in response to treatment (1.31 [0.94 – 1.82]; p=0.034)

EASL. J Hepatol 2017;66:1047
Lee. Hepatology 2012;55:965

Post-TIPS HE

- L-ornithine-L-aspartate (LOLA)

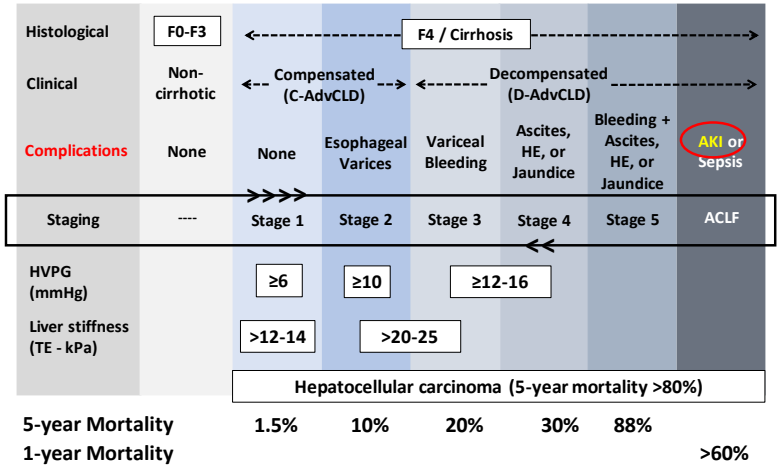


Pharmacologic intervention	Direct estimate, OR (95% CI)	Network estimate, OR (95% PI)	Quality of evidence
LAC vs placebo	**0.21 (0.08–0.58)**	**0.22 (0.09–0.52)**	Moderate
LOLA vs placebo	**0.19 (0.05–0.77)**	**0.19 (0.04–0.91)**	Moderate
RIF vs placebo	0.38 (0.06–2.43)	0.44 (0.09–2.11)	Low
PRO vs placebo	**0.24 (0.09–0.62)**	**0.27 (0.11–0.62)**	Low
RIF vs LAC	1.96 (0.17–22.30)	2.04 (0.39–10.54)	Very low
PRO vs LAC	1.25 (0.49–3.16)	1.22 (0.52–2.85)	Very low
LOLA vs LAC		0.87 (0.15–5.20)	Very low
RIF vs LOLA	–	2.33 (0.26–21.19)	Very low
PRO vs LOLA	–	1.40 (0.24–8.25)	Very low
PRO vs RIF	–	0.60 (0.11–3.31)	Very low

LOLA presumably as effective as lactulose for OHE breakout

Dhiman. Clin Gastroenterol Hepatol;in press

Objectives



Acute kidney injury (AKI) in cirrhosis

- ICA – AKI criteria
  - AKI-ICA: acute kidney injury, International Club of Ascites

	Definition		
AKI	• **↑ sCr ≥0.3 mg/dL in last 48 hours** • **↑ sCr ≥50% from baseline within last 7 days***		
AKI Staging	Stage 1 • sCr ≥0.3 mg/dL or • x1.5-2 baseline	Stage 2 • >x2-3 baseline	Stage 3 • >x3 baseline • sCr ≥4.0 or Dialysis

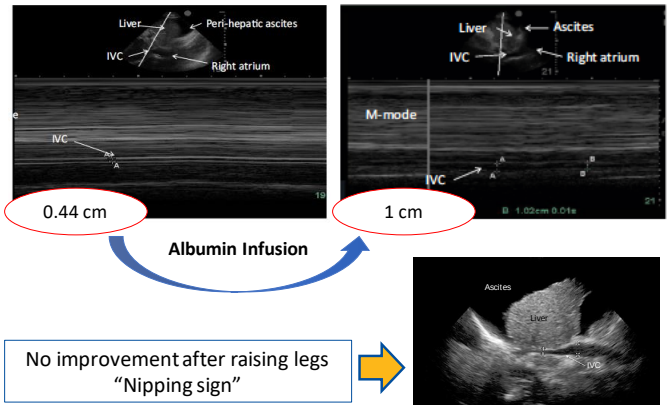
**sCr obtained up to 3 months before AKI admission could be used instead*

All proportional changes, no fixed threshold (i.e., 1.5 mg/dL)

Angeli. J Hepatol 2015;62:968

Volume responsiveness in AKI

- No accurate method to detect fluid intravascular volume in cirrhosis



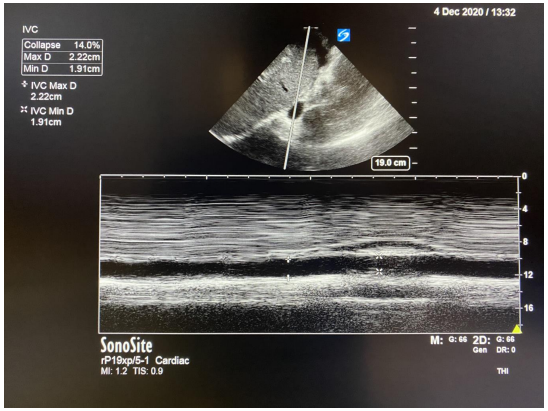
No improvement after raising legs
"Nipping sign"

Volume status adjudication	
Fluid-depleted IVC diameter IVC collapsibility	<1.3 cm >40%
Fluid-repleted IVC diameter IVC collapsibility	>1.3 cm >40%
Fluid-expanded IVC diameter IVC collapsibility	>2 cm <40%
Intra-AB HTN IVC diameter IVC collapsibility	<1.3 cm <40%

Huggins. Am J Med Sci 2016;351:55
Velez. Am J Nephrol 2019;50:204

Volume responsiveness in AKI

- Patient with refractory ascites on diuretics admitted for AKI (Cr 3.9 and ↑)



UNa 11
FEUrea 12.5%
IV Albumin (48-h challenge)
Serum Alb 3.7 g/dL

Volume-expanded
Thus, stopped albumin

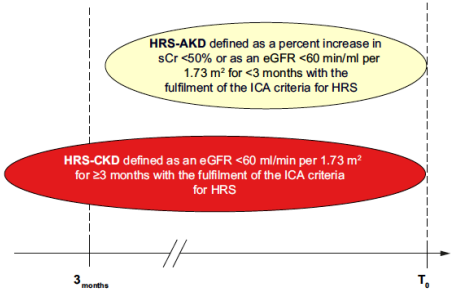
Non-acute (chronic) kidney injury in cirrhosis

- Non-acute kidney injury (NAKI)

HRS - NAKI

HRS – AKD (eGFR <60)

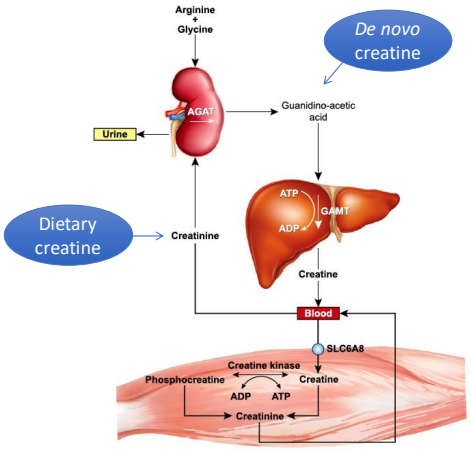
HRS – CKD (eGFR <60)

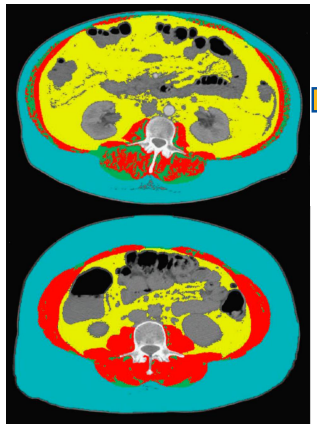


Fixed threshold (greatly affected by skeletal muscle mass loss)

Angeli. J Hepatol 2019;71:811

Creatinine overestimates GFR in cirrhosis



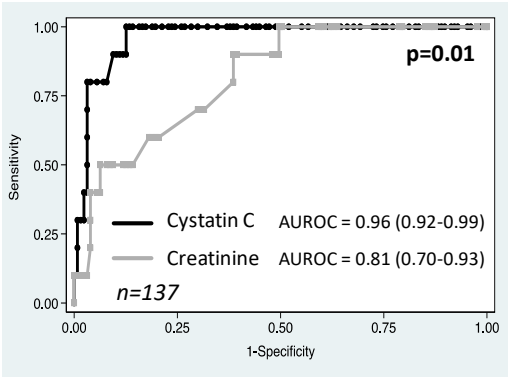


More severe kidney injury than Cr estimates

Francoz. J Hepatol 2010;52:605

Acute kidney injury (AKI) in cirrhosis

- GFR <60 mL/min using iothalamate clearance as reference



Cystatin C better predicts mortality (vs. Cr)

Cystatin C better predicts HD or SLKT (vs. Cr)

Useful for both females and males (unlike Cr)

Personal communication. Dr. Stevan Gonzalez

Simultaneous Liver Kidney Transplantation

- Change in UNOS Policy since August 10, 2017

CKD (eGFR <60 for >90 d)

At least one

1. Regular dialysis for ESRD
2. At KT registration, eGFR <30
3. Post-registration, eGFR <30

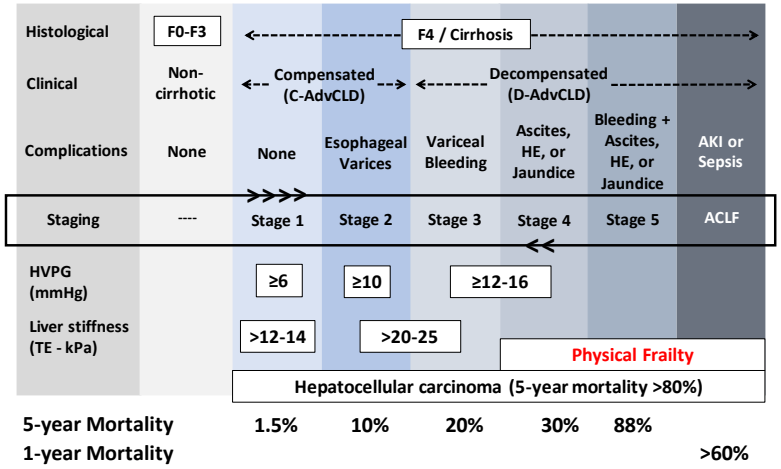
Sustained AKI

At least one

1. On dialysis (q/week) for last 6 weeks
2. eGFR <25 (q/week) for last 6 weeks

UNOS Policy 9.7

Objectives



Frailty in inpatients

- Value of liver frailty index prior to discharge from hospital
  - 211 patients from 3 centers (UPMC, UPenn, UCSF)

	Non-home discharge		All-cause mortality	
	Model 1 (LFI >4.5 vs ≤4.5)	**Model 2 (LFI per 1-point ↑)**	**Model 1 (LFI >4.5 vs ≤4.5)**	**Model 2 (LFI per 1-point ↑)**
	aOR (95% CI)	*aOR (95% CI)*	*sHR (95% CI)*	*sHR (95% CI)*
Age	1.04 (1.00-1.08)	1.02 (0.98-1.07)	1.03 (1.00-1.07)	1.03 (1.00-1.06)
Frailty	**1.88 (0.74-4.78)**	**1.92 (1.22-3.01)**ǂ	**2.20 (1.03-4.70)**ǂ	**1.52 (1.09-2.14)**ǂ
MELD-Na	1.05 (1.00-1.09)ǂ	1.04 (0.99-1.09)	1.03 (1.00-1.06)	1.03 (0.99-1.06)

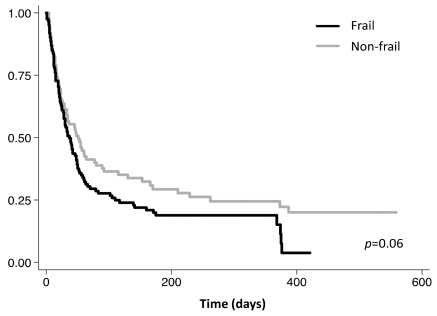
NSBB associated with worse frailty metrics

Serper & Tao. *Submitted for publication*

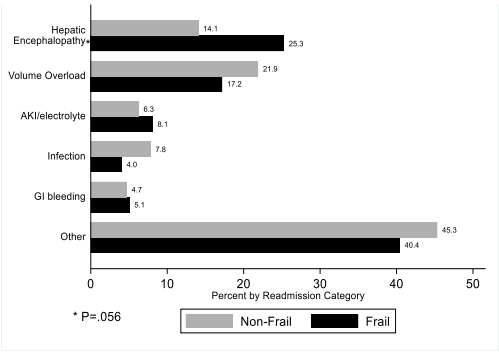
Frailty in inpatients

- Value of liver frailty index prior to discharge from hospital

Clear risk trend for readmission



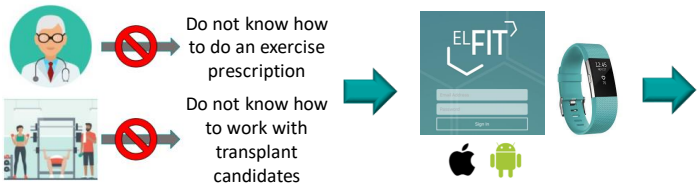
Increased HE readmission rate

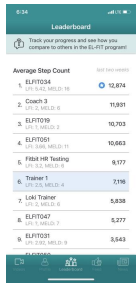


Serper & Tao. *Submitted for publication*

Frailty in inpatients

- Value of liver frailty index prior to discharge from hospital
  - Closer follow-up in clinic
  - Referral to a rehabilitation program





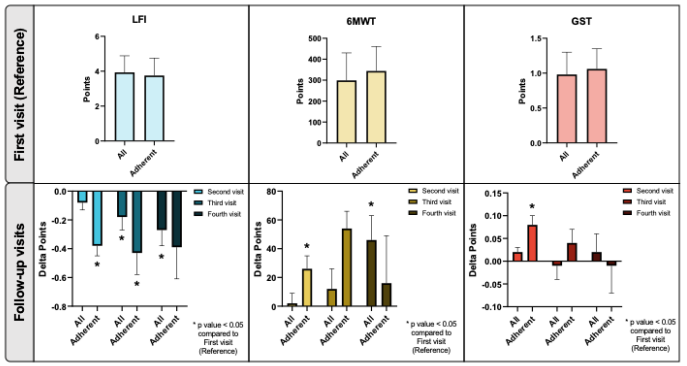
"Leaderboard" showing a frail cirrhotic with MELD score of 16 leading with >12,500 steps/day for more than 14 days

www.el-fit.pitt.edu

Duarte-Rojo. Liver Transpl;in press

Value of rehabilitation in frailty with cirrhosis

- Improvement in LFI and 6MWT mainly in adherent patients (n=517)



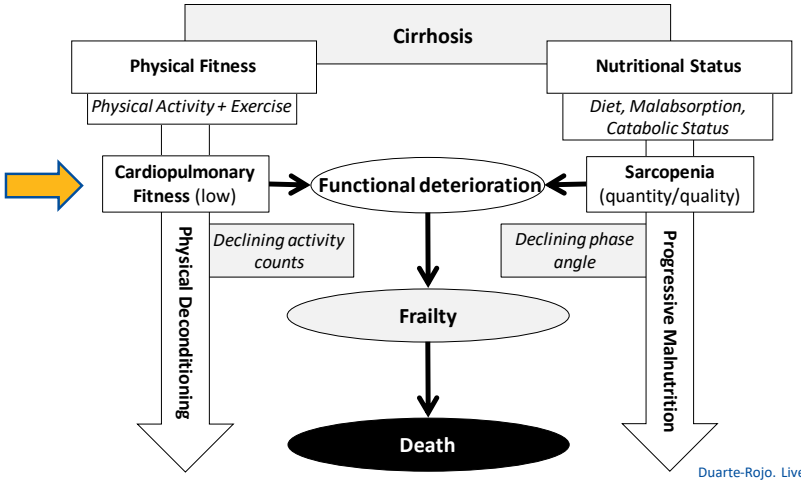
LFI decreases by 0.3 to **0.4** by second visit

6MWT increases by **45 m** by third visit

NSBB associated with worse frailty metrics

Visina & Lin. Manuscript in preparation

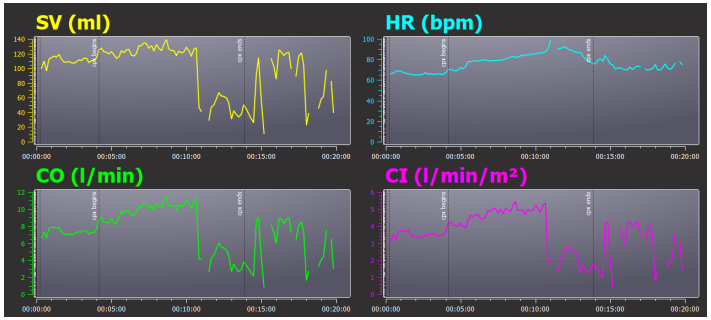
Frailty as an expression of decreased reserve



Duarte-Rojo. Liver Transpl 2018;24:122

Frailty and cardiomyopathy

- Cardiopulmonary exercise testing and impedance cardiography



LFI: 4.09	6MWT: 276	Gait speed: 0.66

Cirrhotic cardiomyopathy

- New diagnostic criteria

a. World Congress of Gastroenterology Criteria (2005)

Systolic Dysfunction	Diastolic Dysfunction	Supportive Criteria
Any of the following • Blunted contractile response on stress testing • LV ejection fraction <55%	Any of the following • Deceleration time >200 milliseconds • Isovolumetric relaxation time >80 milliseconds • E/A <1	• Electrophysiological abnormalities • Abnormal chronotropic response • Electromechanical uncoupling • Prolonged QTc interval • Enlarged left atrium • Increased myocardial mass • Increased BNP • Increased proBNP • Increased troponin I

b. Proposed criteria by the Cirrhotic Cardiomyopathy Consortium (2019)

Systolic Dysfunction	Advanced Diastolic Dysfunction†	Areas for Future Research Which Require Further Validation
Any of the following • LV ejection fraction ≤50% • Absolute* GLS <18% or >22%	≥3 of the following • Septal e' velocity <7 cm/second • E/e' ratio ≥15 • LAVI >34 mL/m² • TR velocity > 2.8 m/second‡	• Abnormal chronotropic or inotropic response§ • Electrocardiographic changes • Electromechanical uncoupling • Myocardial mass change • Serum biomarkers • Chamber enlargement • CMRI‖

Izzy. Hepatology 2020;71:334

Cirrhotic cardiomyopathy

- TIPS and cirrhotic cardiomyopathy
  - Female 67 yo with decompensated cirrhosis, presents with severe SOB post-TIPS

TTE 10/09/2020	
EF	68%
RVSP	26 mmHg (2.8 m/s)
LAVI	42 mL/m²
RA area	normal
e'	7
E/e'	18
Diastolic Dysf.	Grade 2

8 mm TIPS
Pre-PPG: 15 mmHg
Pre-PPG 6 mmHg

11/12/2020

TTE 11/09/2020	
EF	55-60%
RVSP	56 mmHg (3.2 m/s)
LAVI	35 mL/m²
RA area	dilated
e'	7
E/e'	20
Diastolic Dysf.	Grade 3

Izzy. Hepatology 2020;71:334

Apart from COVID, some other new things…

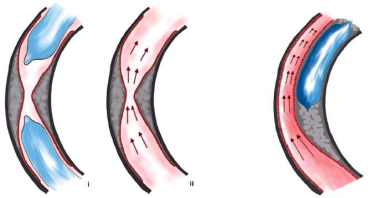
- Use NILDA to risk-stratify patients with clinically significant portal hypertension
- NSBB are still key in the management of cirrhosis (bleeding, ascites, mortality)
- Beware of therapeutic window for NSBB decompensated patients (MAP?)
- Preemptive TIPS in acute variceal bleeding if CTP B + active bleeding or CTP C
- Mind the risk for post-TIPS HE and try to prevent it by using 8 mm TIPS
- For HE, OPA has not made it to market, but for now can use LOLA (supplement)
- In AKI, volume responsiveness is key and IVC US is an emerging resource
- Cystatin C is a better marker of kidney function than creatinine (SLKT)
- Frailty assessment in inpatients can help better triage care transitions
- Cardiomyopathy is an uncommon yet overlooked condition, use novel criteria

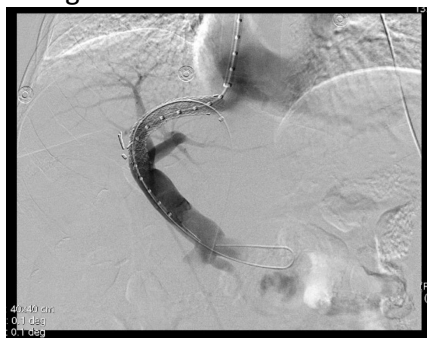
Thanks…

duarterojoa@upmc.edu

Managing post-TIPS refractory HE

- Reduce the size of shunt and increase the gradient

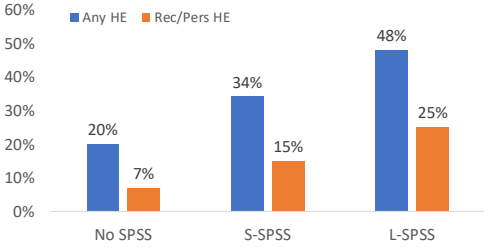


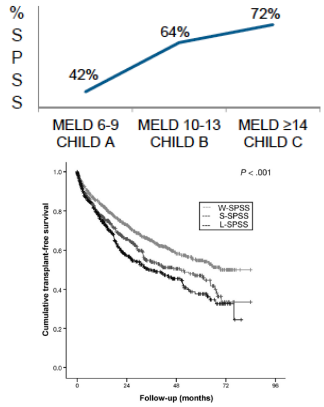


Pereira. Cardiovasc Intervent Radiol 2016;39:170

Spontaneous shunts & HE

- 1729 patients with cirrhosis
  - Large SPSS 28% (≥8 mm) – splenorenal
  - Small SPSS 32% (<8 mm) – paraumbilical





Simon-Talero. Gastroenterology 2018;154:1694