

# Limits of liver resection for HCC

Preoperative functional liver assessment

Dr. Bart Bracke

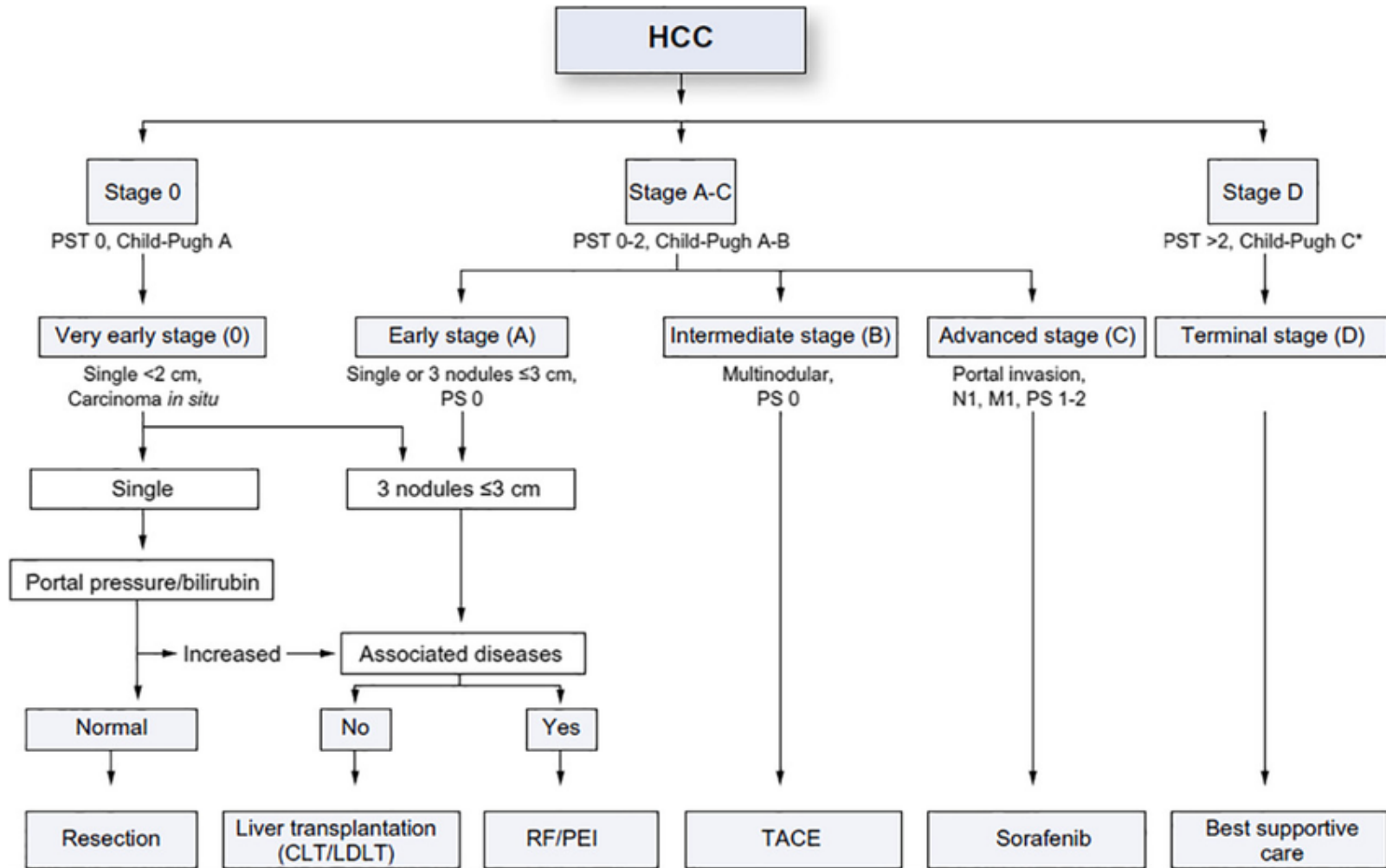
Prof. Dr. Thiery Chapelle

Hepatobiliary, transplantation and endocrine surgery

Universitair Ziekenhuis Antwerpen



# BCLC criteria for HCC management (Barcelona Clinic Liver Cancer)



# Liver resection in cirrhosis

## Main risks of hepatectomy in cirrhosis

- Intraoperative bleeding
  - Distorted vascular anatomy
  - Portal hypertension
  - Trombocytopenia
  - Coagulopathy
- **Post-hepatectomy liver failure (PHLF)**
- Ascites, bacterascites
- Malnutrition

## Contributing to PHLF in cirrhosis:

### Patient related

- Age
- Diabetes mellitus
- Obesity (BMI)

### Liver related

- Steatosis / Steatohepatitis
- Chemotherapy associated liver injury
- Cholestasis
- **Fibrosis**
- **Cirrhosis**

### Surgery related

- Hypotension
- Intraoperative blood loss
- Liver ischemia
- **Remnant liver volume**
- Infection / sepsis
- **Portal hypertension**



# How to diagnose / grade PHLF

- 50/50 criteria (*Belghiti*): PT < 50% and serum bilirubin > 50  $\mu\text{mol/L}$  (= 2,9mg/dL) on POD 5 → 50% 60 day mortality
- Bilirubin > 7mg/dL any POD (*Vauthey*)
- ISGLS Criteria (*International Study Group of Liver Surgery*)

Increased INR and elevated bilirubin on or after POD5

- Grade A: no symptoms, no diagnostics, no treatment, patient on regular ward
  - Grade B: symptoms, non invasive diagnostics and treatment, patient on experienced ward or intermediate care
  - Grade C: critical symptoms, invasive diagnostics and treatment, patient on intensive care unit
- Mortality related ISGLS grading A: 0%, B: 12%, C: 54%



Balzan S. *Ann Surg* 2005;242:824-8.

Mullen, JT. *J Am Coll Surg* 2007 May;204(5):854-62

Rahbari NN. *Surgery* 2011;149:713-24

# Liver dysfunction in cirrhosis

## 1. Reduced hepatocellular function

Synthesis: albumin, clotting factors

Detoxification: bilirubin



Methods for evaluation:

- Child-Pugh score
- MELD score
- ALBI score
- Indocyanine green test
- Hepatobiliary scintigraphy

## 2. Increased fibrosis

Portal hypertension, esophageal varices,  
ascites, splenomegaly, thrombocytopenia



Methods for evaluation:

- Thombocytosis
- APRI score
- Fibrosis-4 score
- Fibroscan
- Hepatic vein pressure gradient



# Prognosis after resection in cirrhosis: impact of dysfunction: bilirubin and portal hypertension

Treatment	Number of Actuarial survival patients		
		1 year	5 years
<b>Surgical resection</b>			
Takayama et al, 1998 <sup>51</sup>			
Very early HCC	15	100%	93%
Overt HCC	52	92%	54%
Fong et al, 1999 <sup>67</sup>	100	83%	42%
Llovet et al, 1999 <sup>43</sup>	77	85%	51%
No portal hypertension, normal bilirubin	35	91%	74%
Portal hypertension, normal bilirubin	15	93%	50%
Portal hypertension, abnormal bilirubin	27	74%	25%
Takayama et al, 2000 <sup>68</sup>			
Arii et al, 2000 <sup>44</sup>			
Stage I HCC <2 cm	1318	96%	72%
Stage I HCC 2-5 cm	2722	95%	58%
Stage II HCC <2 cm	502	92%	55%
Stage II HCC 2-5 cm	1548	95%	58%
Wayne et al, 2002 <sup>69</sup>	249	83%	41%
<b>Liver transplantation</b>			
Iwatzuki et al, 1991 <sup>70</sup>	71	70%	49%
Mazzaferro et al, 1996 <sup>42</sup>	48	84%	74%*
Bismuth et al 1999 <sup>71</sup>	45	82%	74%
Llovet et al, 1999 <sup>43</sup>	79	86%	75%
Intention-to-treat analysis	87	84%	69%
Jonas et al, 2001 <sup>72</sup>	120	90%	71%
Yao et al, 2001 <sup>73</sup>	64	87%	73%
<b>Percutaneous ethanol injection</b>			
Livraghi et al, 1995 <sup>74</sup>			
Child A, HCC <5 cm	293	98%	47%
Child B, HCC <5 cm	149	93%	29%
Lencioni et al, 1997 <sup>75</sup>			
Child A, 1 HCC or 3 nodules <3 cm	127	98%	53%
Child B, 1 HCC or 3 nodules <3 cm	57	88%	28%
Arii et al, 2000 <sup>44</sup>			
Stage I HCC <2 cm	767	96%	54%
Stage I HCC 2-5 cm	587	95%	38%
Stage II HCC <2 cm	426	92%	33%
Stage II HCC 2-5 cm	483	87%	28%
Sakamoto et al, 1998 <sup>63</sup>	88	98%	71%
<b>Radiofrequency ablation</b>			
Rossi et al, 1996 <sup>76</sup>	39	94%	40%
Buscarini et al, 2001 <sup>77</sup>	88	89%	33%

\*4 year survival.

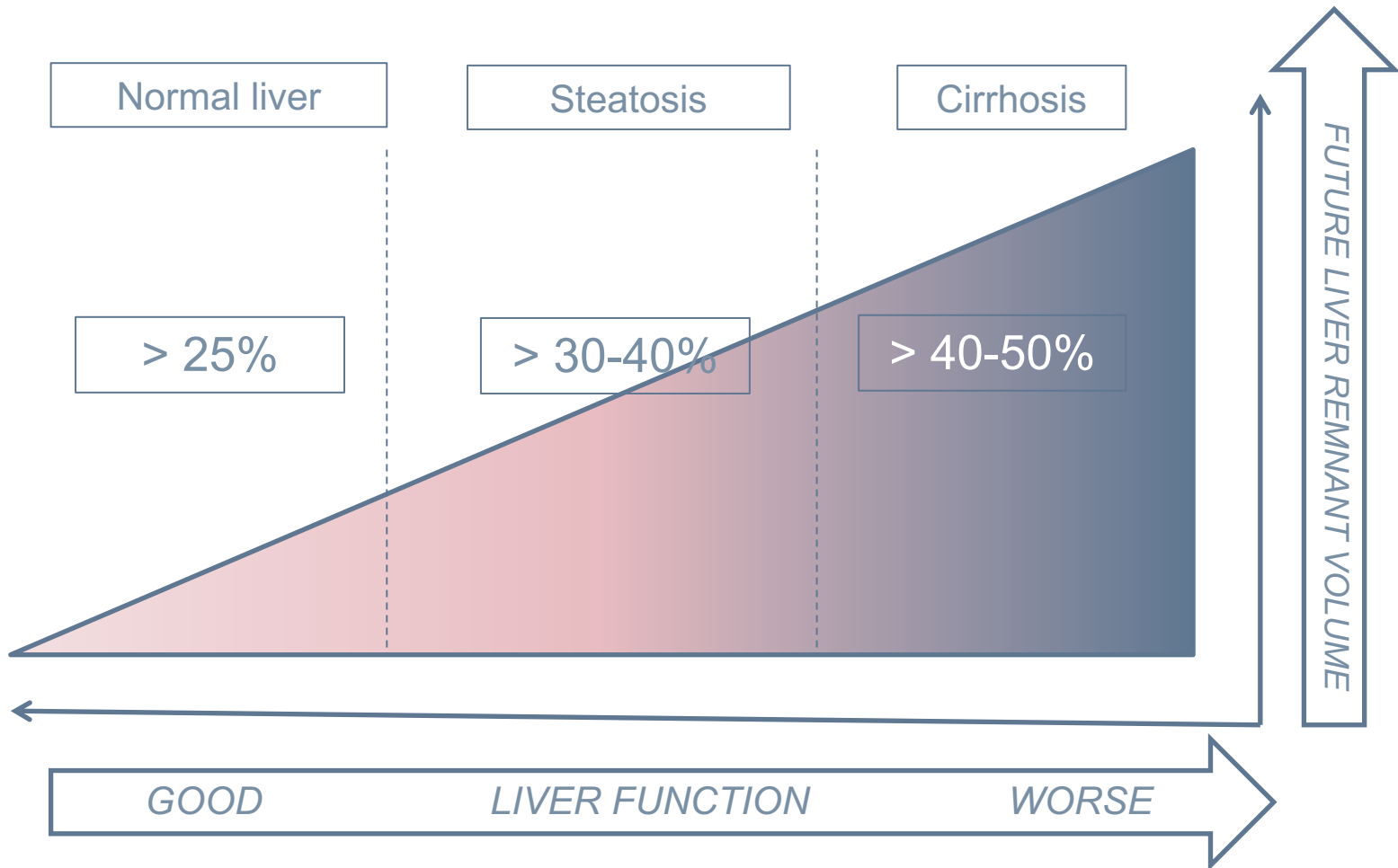


Llovet, Lancet 2003

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# Future liver remnant = critical volume *and* critical function



- (1) Guglielmi A et al, *Dig Surg.* 2012;29(1):6-17.  
(2) Zorzi D et al, *Br J Surg.* 2007;94(3):274-86)

# How to score reduced hepatocellular function?





# Child Pugh score and liver resection in cirrhosis

- 216 patients with cirrhosis, hepatic resection for HCC
- In-hospital mortality Child A: 4.7% ↔ Child B-C: 21.3% (p=0.0003)
  - *Capussotti et al, Eur J Surg Oncol 2005*
- The CP score is the best assessment tool we can now employ
- There is uniform agreement that even segmental resections are not possible in the vast majority of Child Class B patients, CP score 7 to 9
- Discovering which patients in Child Class A are the poor risk is the desired goal
  - *Schneider, Philip D Surg Clin North Am. 2004 Apr;84(2):355-73*



# MELD score and liver resection in cirrhosis

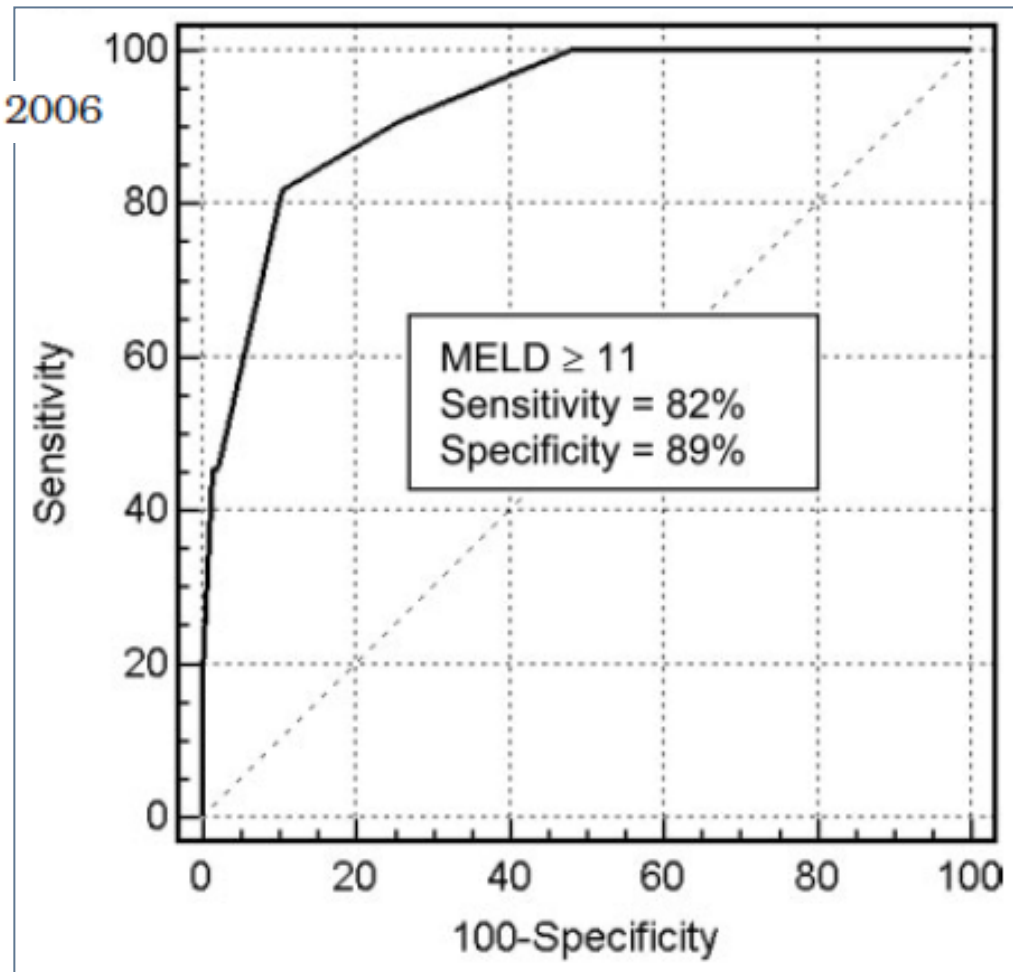
## Impact of Model for End-Stage Liver Disease (MELD) Score on Prognosis After Hepatectomy for Hepatocellular Carcinoma on Cirrhosis

Alessandro Cucchetti, Giorgio Ercolani, Marco Vivarelli, Matteo Cescon, Matteo Ravaioli, Giuliano La Barba, Matteo Zanello, Gian Luca Grazi, and Antonio Daniele Pinna

Department of Surgery and Transplantation, University of Bologna, Policlinico Sant'Orsola-Malpighi, Bologna, Italy

LIVER TRANSPLANTATION 12:966-971, 2006

Receiver operating characteristic (ROC) curve of the MELD score in predicting postoperative liver failure. (AUC 0.92, 95% CI 0.87-0.96)



# ALBI score and liver resection in cirrhosis

- $ALBI = [\log_{10} \text{bilirubin} (\mu\text{mol/L}) \times 0,66] + [\text{albumin (g/L)} \times -0,085]$
- Albumin-bilirubin grade estimates grade of liver dysfunction and is predictive for PHLF
  - Johnson PJ et al, J Clin Oncol 2015 + Andreatos N et al, J Gastrointest Surg 2017
- Albumin-bilirubin score to spleen thickness ratio (ALBI/ST)
- ALBI/ST ratio was a strong risk factor of PHLF in all hepatectomy subgroups.
- In conclusion, the ALBI/ST ratio has a superior predictive ability for PHLF compared with APRI and FIB-4.
  - Zhang ZQ et al, Medecine 2019

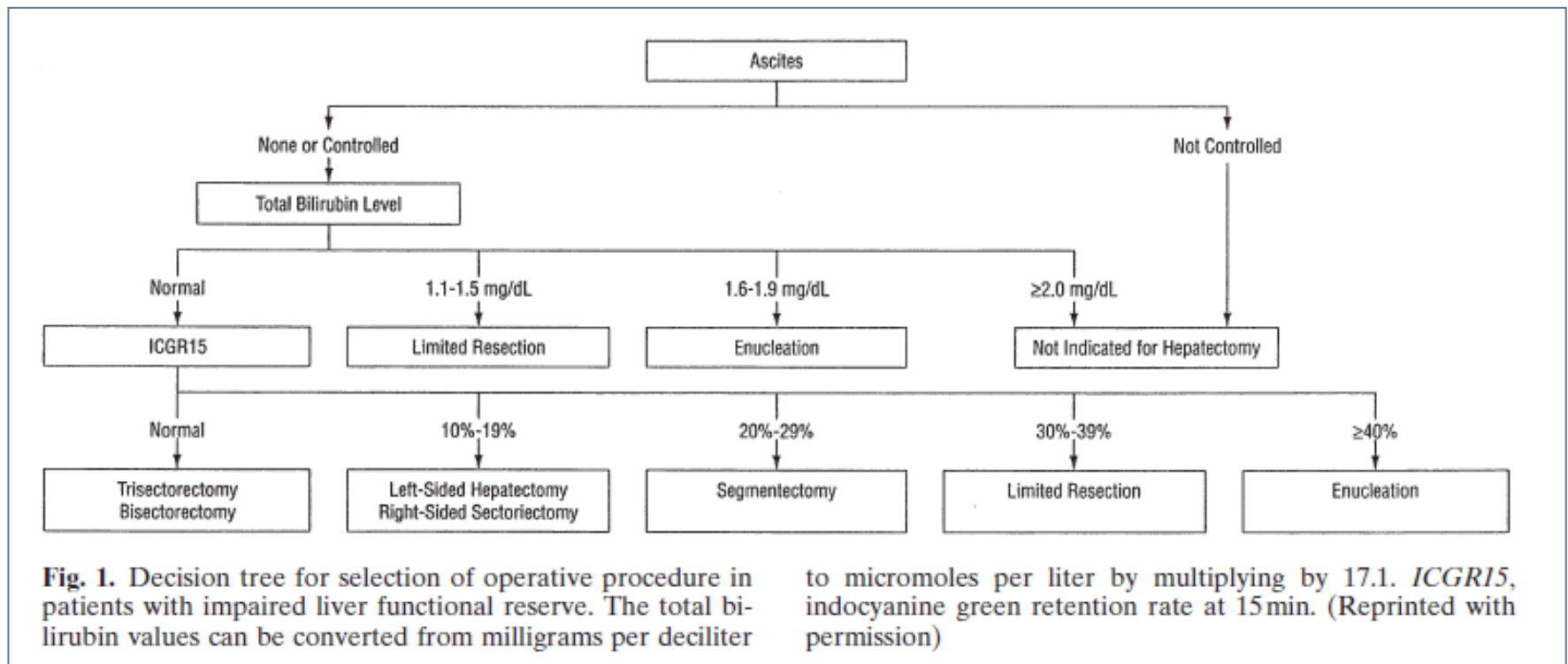


# ICG and liver resection in cirrhosis

## Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test

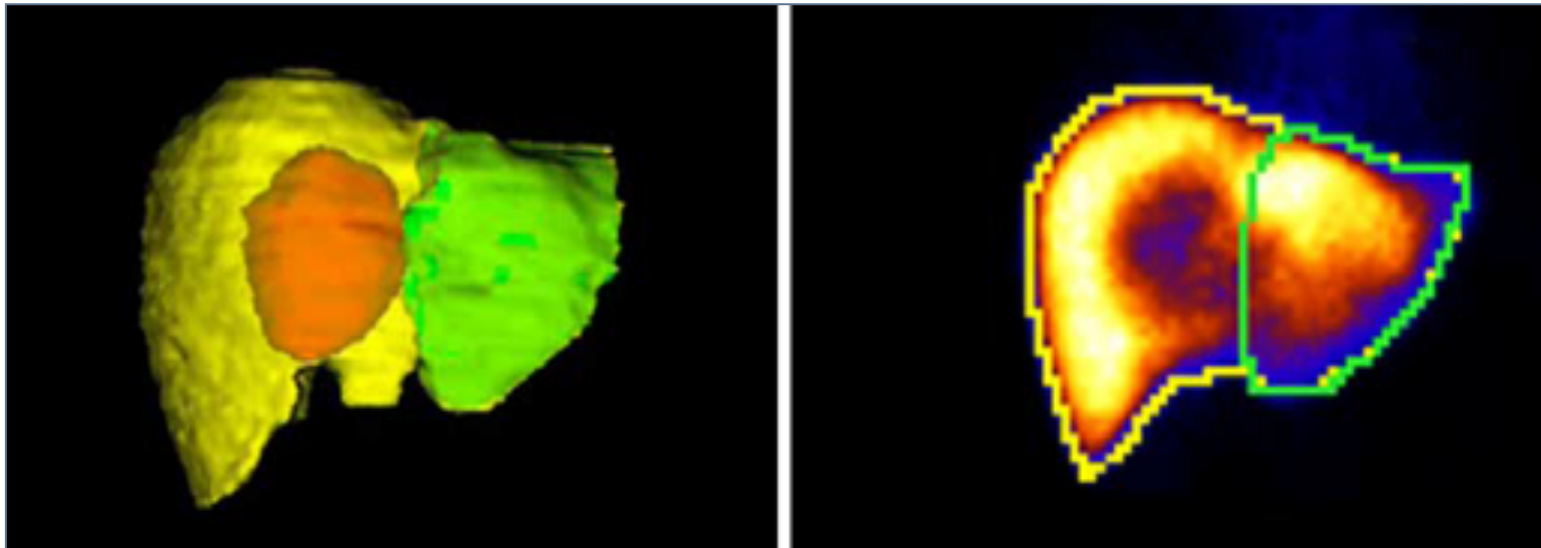
HIROSHI IMAMURA, KEIJI SANO, YASUHIKO SUGAWARA, NORIHIKO KOKUDO, and MASATOSHI MAKUUCHI

Division of Hepato-Biliary-Pancreatic Surgery and Artificial Organ and Transplantation, Department of Surgery, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan



# Hepatobiliary scintigraphy with $^{99m}\text{Tc}$ -mebrofenin and liver resection in cirrhosis

- $^{99m}\text{Tc}$ -mebrofenin circulates in an albumin-bound form
- dissociates from albumin after uptake into hepatocytes
- undergoes biliary excretion without undergoing biotransformation
- similar to ICG also not suitable in cholestatic livers
- has been validated as a tool for measuring the total liver function and functional remnant liver before liver surgery.

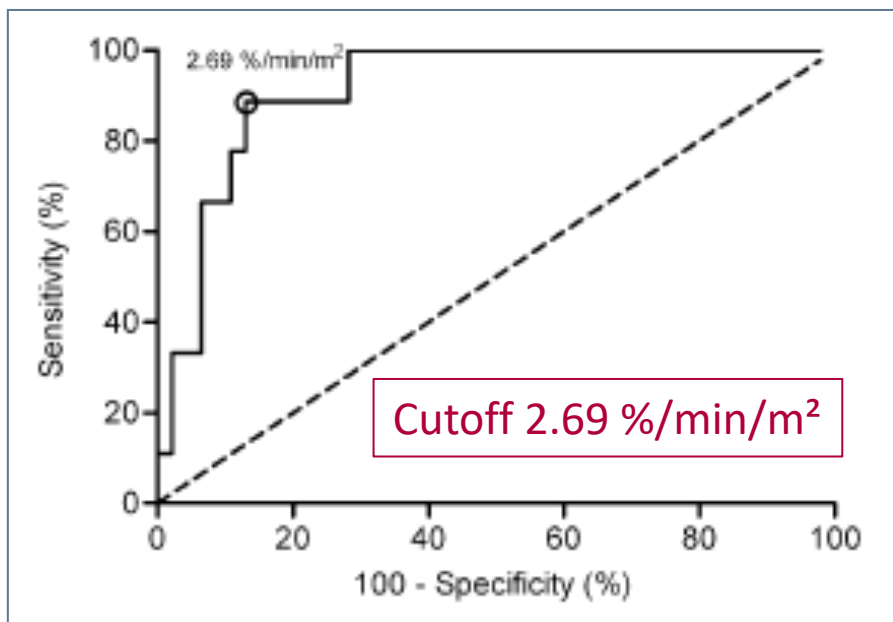


# Hepatobiliary scintigraphy with $^{99m}\text{Tc}$ -mebrofenin: the cutoff's to prevent PHLF in all hepatectomies

## Assessment of Future Remnant Liver Function Using Hepatobiliary Scintigraphy in Patients Undergoing Major Liver Resection

Wilmar de Graaf • Krijn P. van Lienden • Sander Dinant • Joris J. T. H. Roelofs • Olivier R. C. Busch • Dirk J. Gouma • Roelof J. Bennink • Thomas M. van Gulik

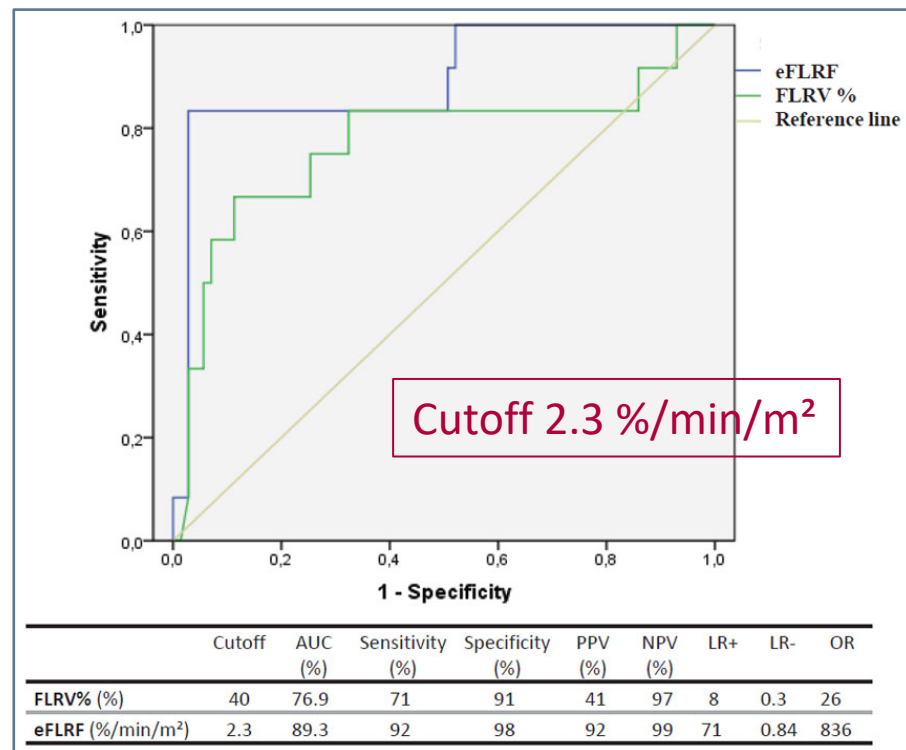
J Gastrointest Surg (2010) 14:369–378



## Future remnant liver function estimated by combining liver volumetry on magnetic resonance imaging with total liver function on $^{99m}\text{Tc}$ -mebrofenin hepatobiliary scintigraphy: can this tool predict post-hepatectomy liver failure?

Thiery Chapelle<sup>1</sup>, Bart Op De Beeck<sup>2</sup>, Ivan Huyghe<sup>3</sup>, Sven Francque<sup>4</sup>, Ann Driessen<sup>5</sup>, Geert Roeyen<sup>1</sup>, Dirk Ysebaert<sup>1</sup>

HPB 2016;18(6):494-503



# Hepatobiliary scintigraphy with $^{99m}\text{Tc}$ -mebrofenin in cirrhosis

- The assessment of hepatobiliary function by Tc-mebrofenin scintigraphy may be a good choice for assessing the severity of liver fibrosis in patients with HCV.
  - *Kula M et al, Nucl Med Commun 2010*



# How to score increased fibrosis?





# Trombocytosis & APRI score and liver resection in cirrhosis

- Preoperative and/or postoperative thrombocytopenia (platelet count below 100 or 150) constitute significant risk factors for PHLF in cirrhotic and non-cirrhotic patients.

- *Meyer, J HPB 2019*

- $$\text{APRI} = \frac{\frac{\text{AST}}{\text{upper limit of normal}}}{\text{platelet count}} \times 100$$

- Score designed for cirrhotic livers, but predicts PHLF in chemo-associated liver injury patients



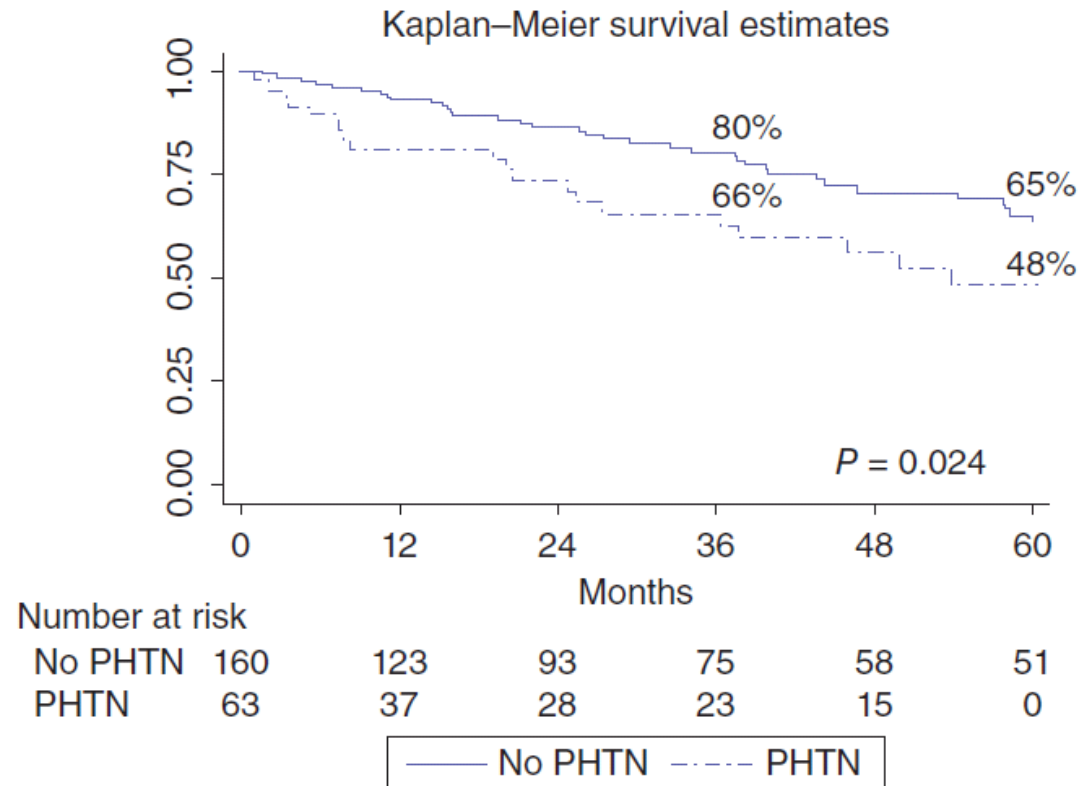
# Fib-4 score & Fibroscan and liver resection in cirrhosis

- $$\text{FIB-4} = \frac{\text{age} \times \text{AST}}{\text{platelet count} \times \sqrt{\text{ALT}}}$$
- The FIB-4 index may be a better predictor of PHLF and overall survival in HCC patients underwent hepatectomy than CP score.
  - *Zhou P et al J Gastroint Surg 2018*
- Liver stiffness measurement by transient elastography has a similar performance to HVPG in predicting decompensation at 3 months after liver resection.
  - *Procopet B et al , Ultrason 2018*
- Liver stiffness measurement is a valid and reliable method for the prediction of PHLF grade A/B among patients with HCC
  - *Han H et al , Eur J Rad 2017*



# Clinical estimation of portal hypertension and liver resection in cirrhosis

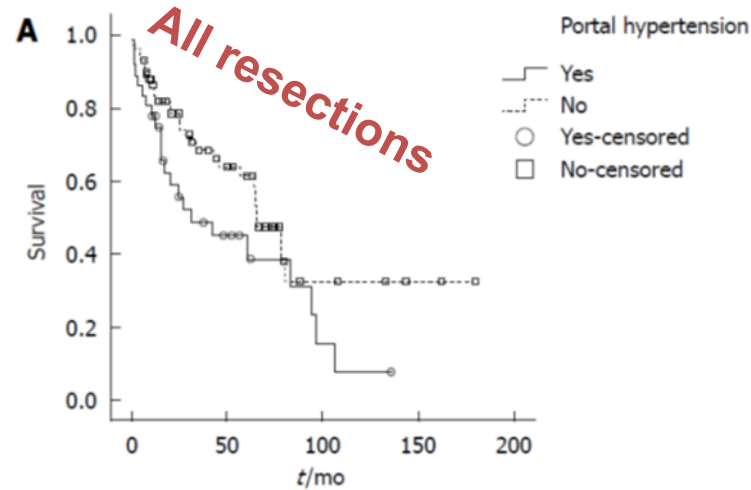
- Esophageal varices
- Splenomegaly
- Platelet count < 100.000
- *Santambrogio R HPB 2013*



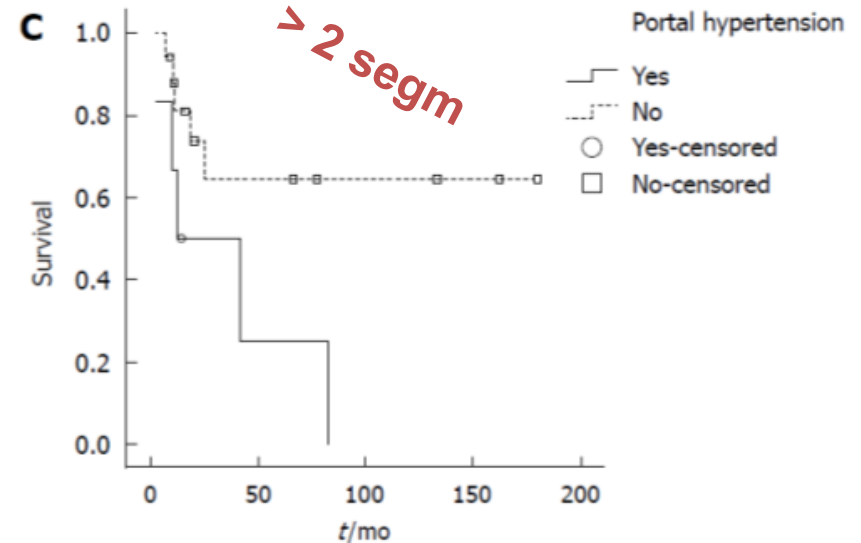
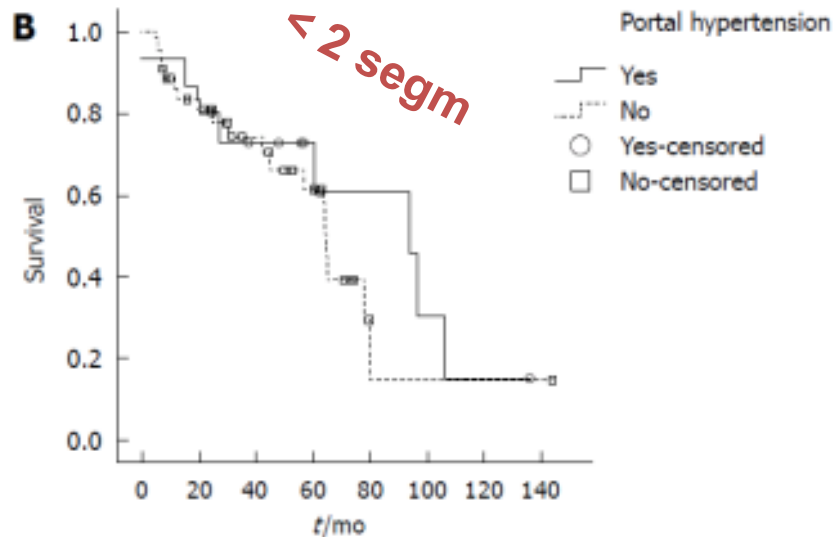
**Figure 1** Overall survival curves of the whole study population of 223 cirrhotic patients undergoing a hepatic resection (HR) for hepatocellular carcinoma (HCC) with the portal hypertension (PHTN) or without PHTN ( $P = 0.024$ )



# Impact of resection < 2 or > 2 segments in clinical portal hypertension



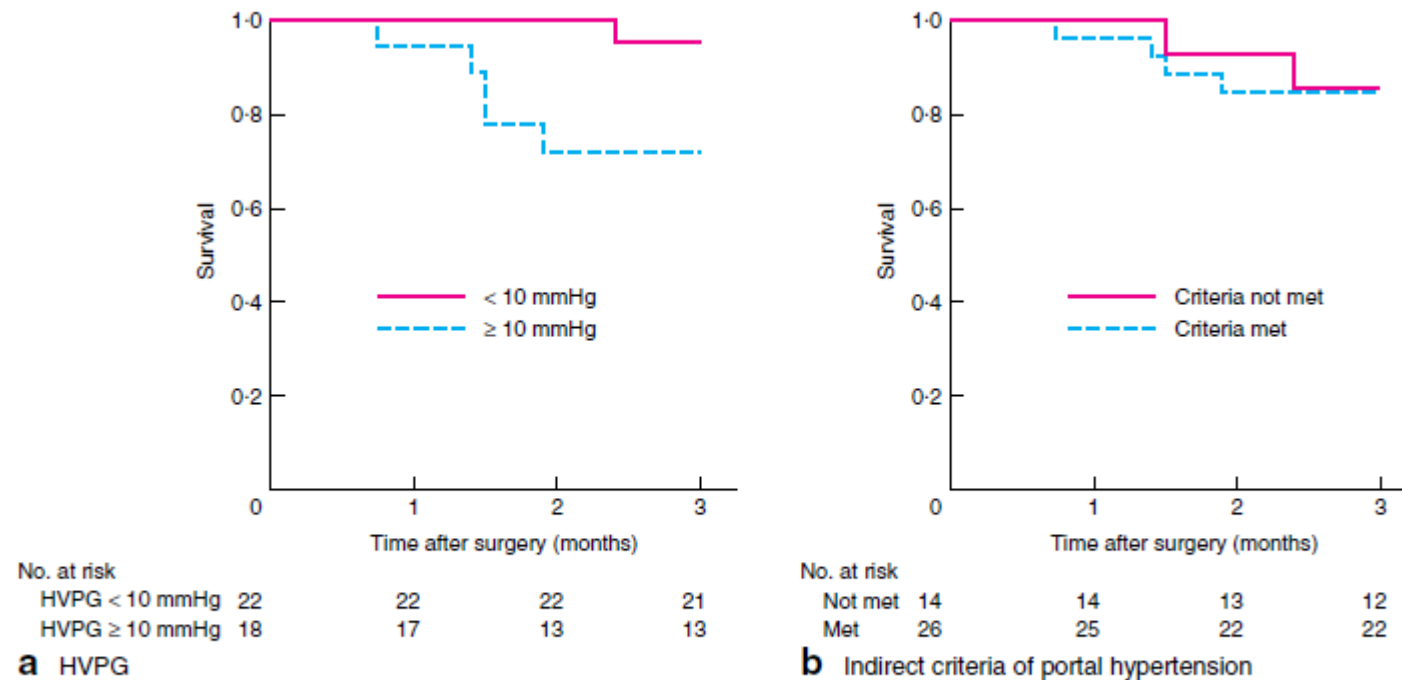
*Ruzzenente A et al, WJG 2011*



# Estimation of hepatic venous pressure gradient better than clinical estimation of portal hypertension

## Hepatic venous pressure gradient in the assessment of portal hypertension before liver resection in patients with cirrhosis

E. Boleslawski<sup>1</sup>, G. Petrovai<sup>1</sup>, S. Truant<sup>1</sup>, S. Dharancy<sup>2</sup>, A. Duhamel<sup>3</sup>, J. Salleron<sup>3</sup>, P. Deltenre<sup>2</sup>, G. Lebuffe<sup>4</sup>, P. Mathurin<sup>2</sup> and F. R. Pruvot<sup>1</sup>



**Fig. 2** Actuarial survival according to **a** hepatic venous pressure gradient (HVPG) and **b** presence of indirect criteria of portal hypertension. **a**  $P = 0.036$ , **b**  $P = 0.879$  (log rank test)



# HVPG and liver resection in cirrhosis

- HVPG  $\geq 10$  mmHg = contraindication for hepatic resection (EASL\* and AASLD guidelines)
- HVPG  $< 10$  mmHg: 90% will not develop decompensation of cirrhosis within 4y \*\*
- Elevated HVPG  $\rightarrow$  negative prognosis of patients with HCC and cirrhosis



- HVPG  $> 10$  mmHg  $\neq$  absolute contraindication for hepatic resection \*\*\*
- Excluding all HVPG  $> 10$  mmHg from hepatic resection, will exclude 25% patients who would benefit of surgery without short-term postoperative complications \*\*\*\*

\* Bruix J, *Hepatology* 2005

\*\* Ripoll C, *Gastroenterol* 2007

\*\*\* Xiaolong Q. et al *Oncotarget*. 2016

\*\*\*\* Cucchetti A, *J of Hepatology* 2016



# Portal hypertension and liver resection

**Table1: Association between elevated HVPG and prognosis of HCC with cirrhosis after hepatic resection**

Study	Inclusion period	Measurements of HVPG	No. of surgical cases	No. of elevated HVPG	Main Endpoints	Conclusions
Boleslawski, 2012 [10]	2007-2009	directly	40	≥10 mmHg 18 (45.0%)	Postoperative liver dysfunction	A raised HVPG was associated with postoperative liver dysfunction and 90-day mortality.
Stremitzer, 2011 [11]	2000-2009	directly	35	≥5mmHg 14 (40.0%)	Postoperative complications and death	HVPG exceeding 5 mmHg was associated with worse liver fibrosis, higher rates of postoperative liver dysfunction and ascites and a longer hospital stay.
Cucchetti, 2016 [12]	2009-2014	directly	70	≥10 mmHg 34 (48.6%)	Post-hepatectomy liver failure defined by the International Study Group of Liver Surgery, 90 day mortality, Detailed clinical evaluation after 3 months	HVPG can be used to stratify the risk of post-hepatectomy liver failure. CSPH was associated with a higher risk of ascetic decompensation. But there was no difference in 1- and 3- survival rates after resection between CSPH group and non-CSPH group.
Ripoll, 2007 [13]	1993-1999	directly	213	≥10 mmHg 134 (62.9%)	Development of clinical decompensation	HVPG can predict clinical decompensation in patients with compensated cirrhosis. Patients without CSPH have a 90% probability of not developing clinical decompensation in a median follow-up of 4 years.
Ishizawa, 2008 [14]	1994-2004	the presence of EV and/or PC of 100,000/L associated with splenomegaly	386	≥10 mmHg 136 (35.2%)	Recurrence, 3-year/5-year mortality	Long-term outcomes were poorer in CSPH group than in the no-CSPH group among patients with Child-Pugh class A cirrhosis but did not differ in two groups among patients with Child-Pugh class B cirrhosis
He, 2015 [17]	2003-2008	if two or more of the criteria were met: 1) PC < 100 × 10 <sup>9</sup> /l and/or white blood cell count < 4 × 10 <sup>9</sup> /l three times in succession, 2) Splenomegaly, 3) Portal vein width > 14 mm or spleen vein width > 10 mm via ultrasound, and 4) EV.	209	≥10 mmHg 102 (48.8%)	Recurrence, Liver decompensation, 5-year mortality	Before propensity score matching, CSPH patients had higher rates of postoperative complication and liver decompensation with similar rates of recurrence-free survival and overall survival. However, after propensity score matching, revealed similar rates of postoperative complication, liver decompensation, recurrence-free survival and overall survival.
Giannini, 2013 [18]	1987-2008	the presence of either EV or gastric varices, portal hypertensive gastropathy, or PC < 100 × 10 <sup>9</sup> /l associated with splenomegaly	152	≥10 mmHg 68 (44.7%)	Death or until December 2008	Presence of CSPH has no influence on survival of HCC patients with well-compensated cirrhosis.



# Portal hypertension and liver resection

**Table 1** Relevant reported studies describing the impact of hepatic venous pressure gradient or portal-hypertension related variables in patients with potentially resectable or resected hepatocellular carcinoma

Ref.	Patients included (n)	Portal hypertension-related variables studied	Outcome
Llovet <i>et al</i> <sup>[3]</sup>	43	HVPG	CSPH independently associated with 5-yr post-operative mortality
Bruix <i>et al</i> <sup>[12]</sup>	29	HVPG	CSPH independently associated with PLF at 3-mo
Berzigotti <i>et al</i> <sup>[13]</sup>	63	Spleen size; platelet count; platelet count/spleen diameter; liver stiffness; LSPS PH risk score	Best single predictor of CSPH: liver stiffness; combination with spleen size and platelet count improved the results (AUROC LSPS 0.852; PH risk score 0.884)
Boleslawski <i>et al</i> <sup>[14]</sup>	43	HVPG Platelet count; spleen size; esophageal varices = indirect signs of PH	CSPH independently associated with increased PLF and 90-d mortality. Indirect signs of PH showed no discriminative ability
Capussotti <i>et al</i> <sup>[15]</sup>	217	Platelet count; spleen size; esophageal varices	PH associated with lower 3-yr and 5-yr survival
Cescon <i>et al</i> <sup>[16]</sup>	90	Liver stiffness; platelet count; spleen size; esophageal varices	LS (but not other signs) independently associated with the risk of PLF
Chen <i>et al</i> <sup>[17]</sup>	190	Intraoperative measurement of PVP	PVP independently associated with PLF on multivariate analysis
Cucchetti <i>et al</i> <sup>[18]</sup>	241	Platelet count; spleen size; esophageal varices	PH associated with lower 3-yr and 5-yr survival, but not after adjusting for MELD, albumin and extent of resection no CSPH associated with increased risk of morbidity
Figueras <i>et al</i> <sup>[19]</sup>	39	HVPG	CSPH associated with increased risk of morbidity
Giuliante <i>et al</i> <sup>[20]</sup>	588	Platelet count; spleen size; esophageal varices	PH independently associated with increased mortality
Imamura <i>et al</i> <sup>[21]</sup>	532	Varices, hypersplenism or hepatofugal portal flow	PH associated with a higher risk of post-operative ascites
Ishizawa <i>et al</i> <sup>[22]</sup>	203	Platelet count	Platelet count < 100 × 10 <sup>3</sup> /mL independently associated with PLF
Kim <i>et al</i> <sup>[23]</sup>	72	Liver stiffness	LS predicted PLF with good accuracy; LS better than ICG15
Llop <i>et al</i> <sup>[24]</sup>	79	Liver stiffness	CSPH predicted with good accuracy
Ishizawa <i>et al</i> <sup>[25]</sup>	434	Platelet count; spleen size; esophageal varices	PH associated with lower 3-yr and 5-yr survival

HVPG: Hepatic venous pressure gradient; PH: Portal hypertension; LS: Liver stiffness; PVP: Portal vein pressure; PLF: Post-operative liver failure; CSPH: Clinically significant PH (HVPG ≥ 10 mmHg); AUROC: Area under receiver operating characteristic curve; MELD: Model for end-stage liver disease.





# Can HBS predict clinical portal hypertension in cirrhosis?

Median HBS, HBS<sup>BSA</sup> and MELD score for HVPG < or ≥ 10mmHg in Child-Pugh A and in Child-Pugh B/C.

		HVPG		p
		< 10mmHg	≥ 10mmHg	
<b>Child-Pugh A</b>	(n)	31	17	
HBS	%/min	9.18 (4.61 - 13.88)	7.19 (2.43 - 10.30)	0.001
HBS <sup>BSA</sup>	%/min/m <sup>2</sup>	5.23 (2.56 - 7.95)	3.28 (1.13 - 5.20)	<0.001
MELD		8 (3 - 14)	8 (6 - 14)	0.974
<b>Child-Pugh B/C</b>	(n)	14	37	
HBS	%/min	3.84 (1.81 - 10.60)	2.48 (0.41 - 10.00)	0.005
HBS <sup>BSA</sup>	%/min/m <sup>2</sup>	2.12 (0.97 - 6.76)	1.23 (0.17 - 5.34)	0.003
MELD		11.50 (6 - 18)	16 (2 - 28)	0.005



# Recent insights

- MELD score, bilirubin, alpha-fetoprotein and platelet count showed significant predictive value for PHLF/I (all  $p < 0.05$ ). A composite score based on these factors serves as guideline for physicians to better select patients undergoing extensive resections to minimize PHLF.
  - *Chin KM et al, Ann Hepatobiliary Pancreat Surg. 2018*
- Laparoscopy reduces the risk of PHLF in cirrhotic liver
- Remnant of total liver volume, platelets and intraoperative blood loss are other predictors of PHLF
- Predictive models available at: <https://prodeau.shinyapps.io/shiny/>.
  - Prodeau M et al, J Hepatol 2019



# Functional limits in liver resection in cirrhosis

## Conclusions

- PHLF after hepatectomy for HCC in cirrhotic liver is multifactorial: reduced hepatocellular function, increased fibrosis, portal hypertension, future volume/function of remnant, open vs laparoscopic resection, blood loss,...
- No good score/flow chart for cirrhotic patients

Editorial



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### **Towards a personalized approach to hepatic resection in cirrhotic patients**

Alessandro Vitale<sup>1,\*</sup>, Pietro Majno-Hurst<sup>2</sup>

<sup>1</sup>Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy; <sup>2</sup>Department of Surgery, Ente Ospedaliero Cantonale, Università della Svizzera Italiana, Lugano, and Departments of Surgery and Transplantation, University Hospitals of Geneva, Switzerland

See Article, pages 920–929



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# But for now to stay on the safe side:

Resection of HCC in cirrhosis only if:

- Enough future liver remnant, evaluated by liver volumetry and liver function
- compensated cirrhosis in Child-Pugh A patient
- Hepatic Venous Pressure Gradient < 10 mmHg



Thank you!

