

PULMONARY VASCULAR COMPLICATIONS OF LIVER DISEASE

Michael B. Fallon, MD.

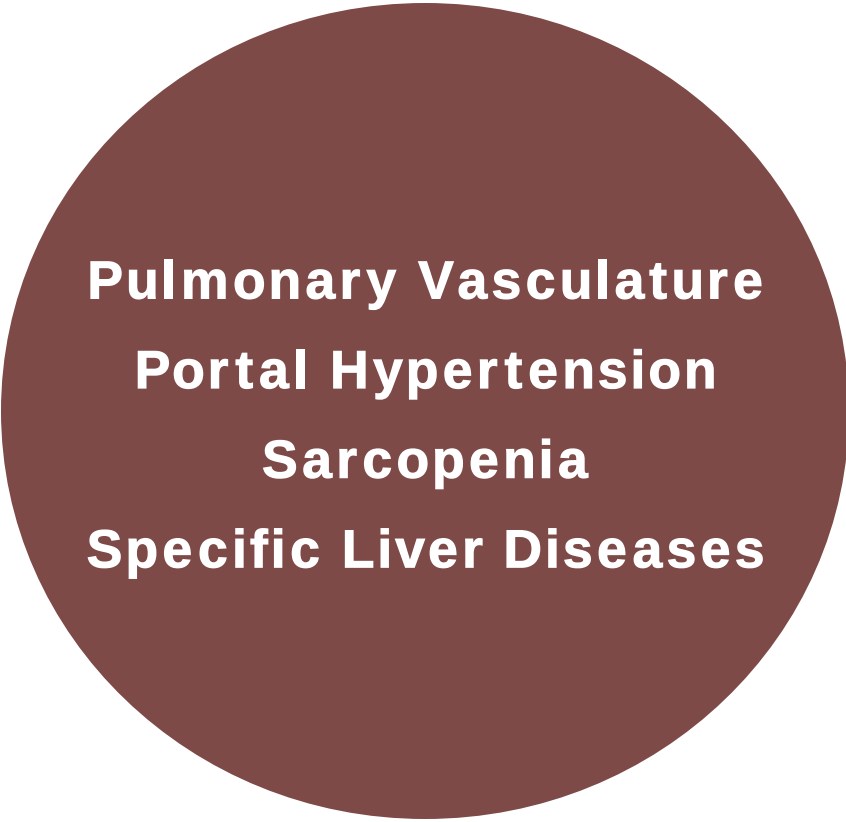


THE UNIVERSITY OF ARIZONA
College of Medicine
Phoenix

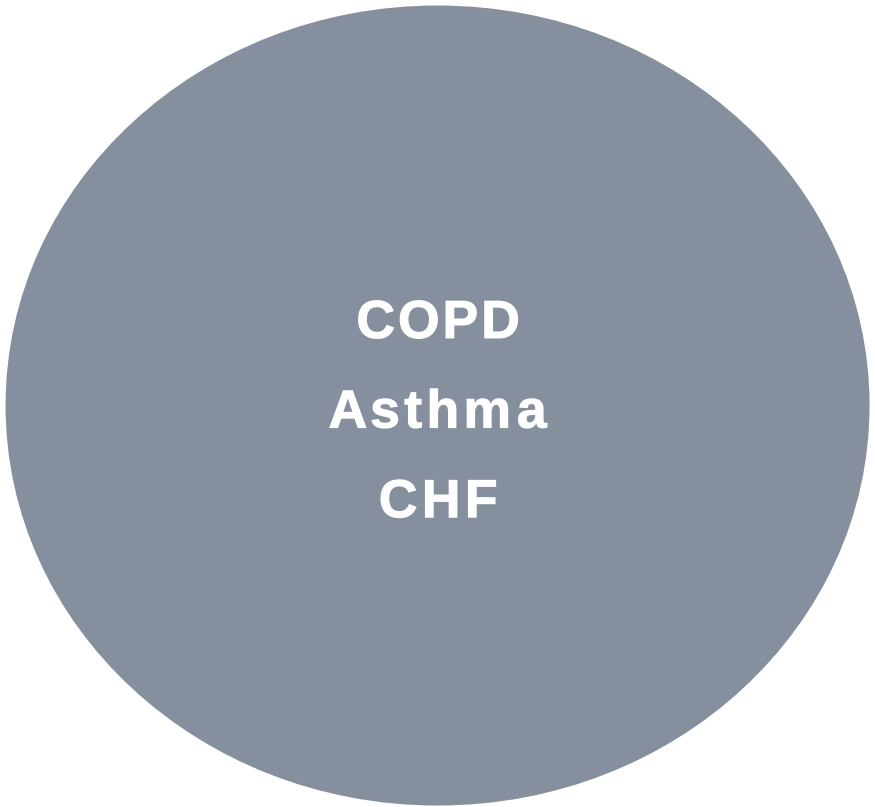
NO DISCLOSURES

DYSPNEA AND HYPOXEMIA IN CIRRHOSIS

RELATED TO CHRONIC LIVER DISEASE



**Pulmonary Vasculature
Portal Hypertension
Sarcopenia
Specific Liver Diseases**



**COPD
Asthma
CHF**

INTRINSIC LUNG DISEASE

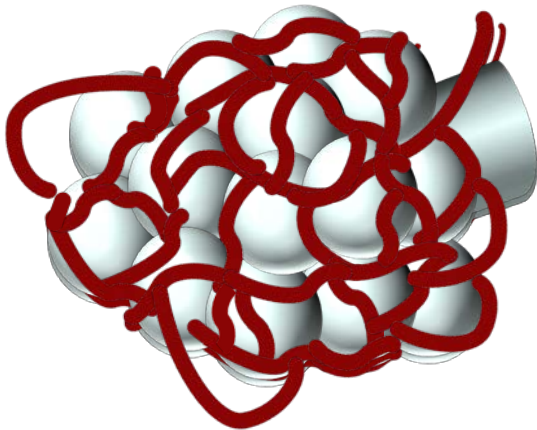
Pulmonary vascular disorders	20-30%
Chronic obstructive pulmonary disease	17%
Asictes, hepatic hydrothorax	5%
Congestive heart failure	5%
Specific liver diseases	3%
Deconditioning	2%
Asthma	1%

Cirrhosis
Hepatic injury
Portal hypertension



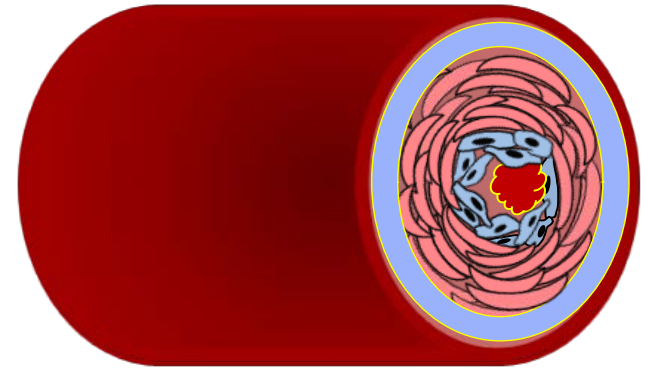
LUNG

HPS



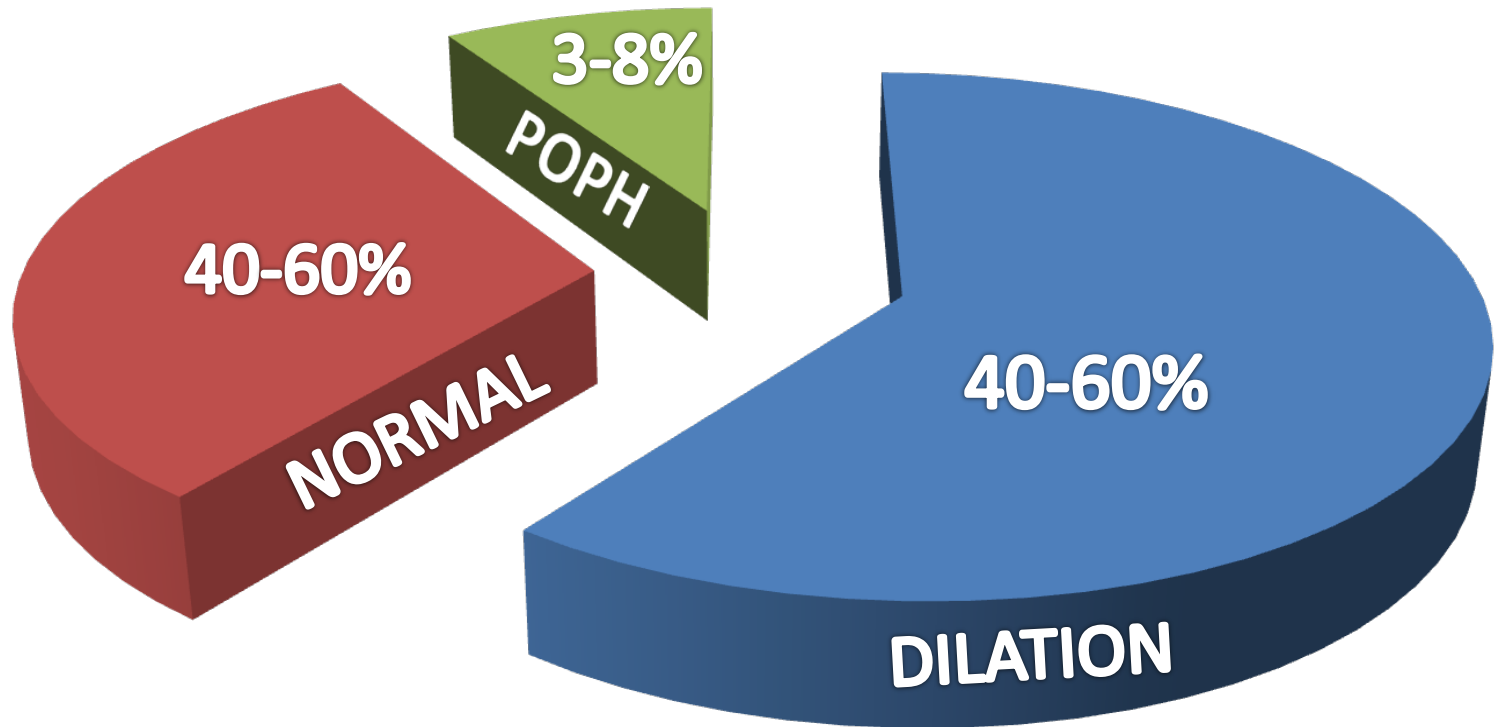
Vasodilatation and
Angiogenesis
in microvasculature

POPH

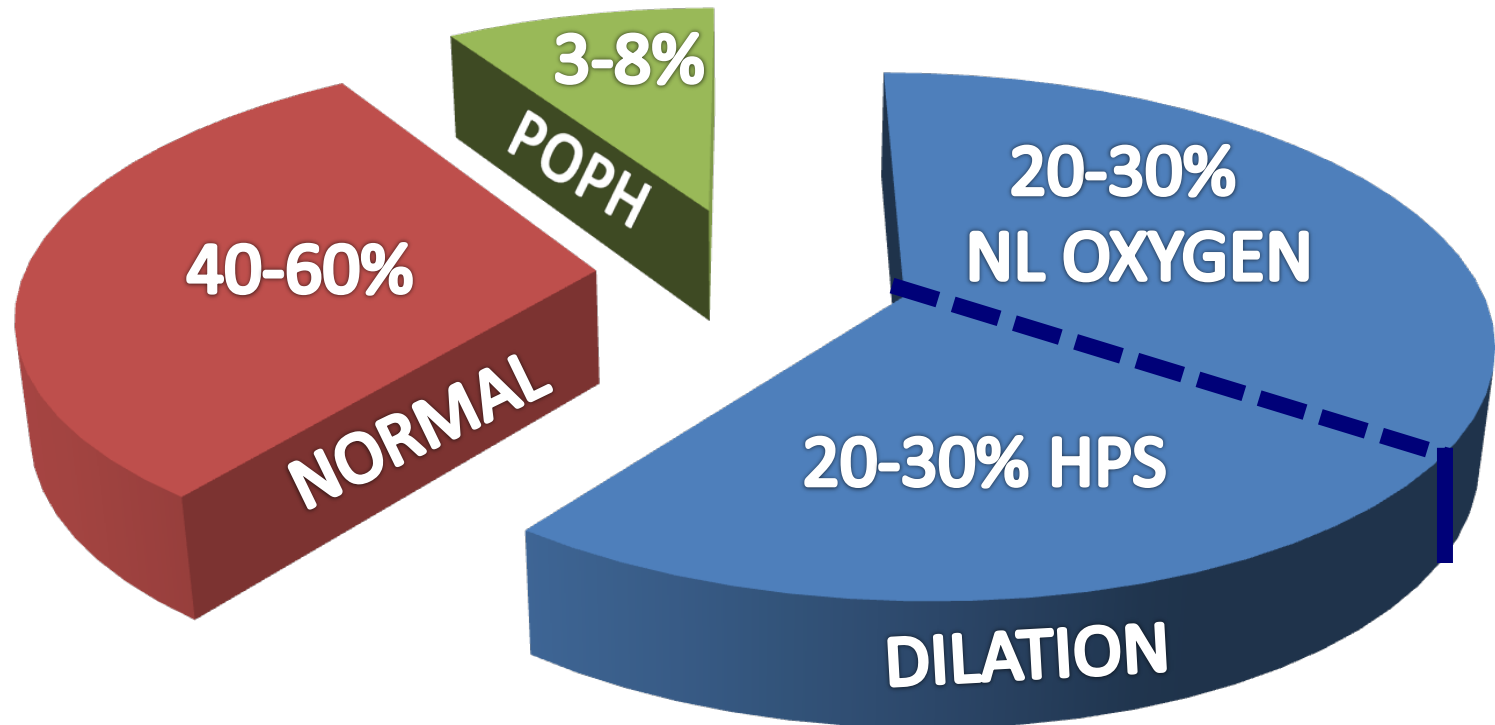


Vasoconstriction and
remodeling in resistance
vessels

PULMONARY VASCULATURE IN CIRRHOSIS



PULMONARY VASCULATURE IN CIRRHOSIS



HEPATOPULMONARY SYNDROME (HPS)

HPS: DEFINITION

- **Cirrhosis and/or portal hypertension**
- **Arterial $pO_2 < 70\text{mmHg}$ or A-a $PO_2 > 15\text{ mmHg}$**
- **Intrapulmonary vasodilatation**
- **No marked cardiopulmonary pathology**

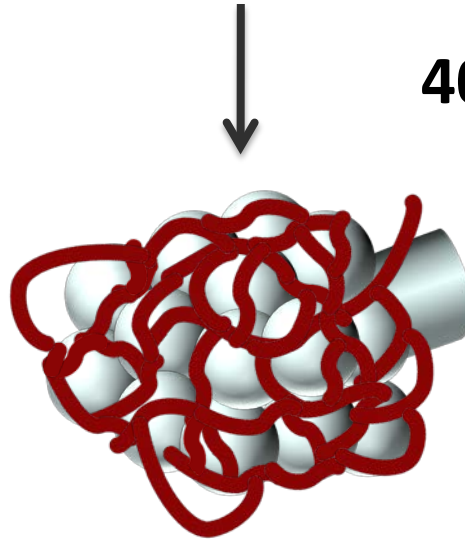
- ❖ Portal Hypertension
- ❖ Cirrhosis
- ❖ Portosystemic shunting

Contrast



Sensitive
Specific
Other cardiac
data

40-60%

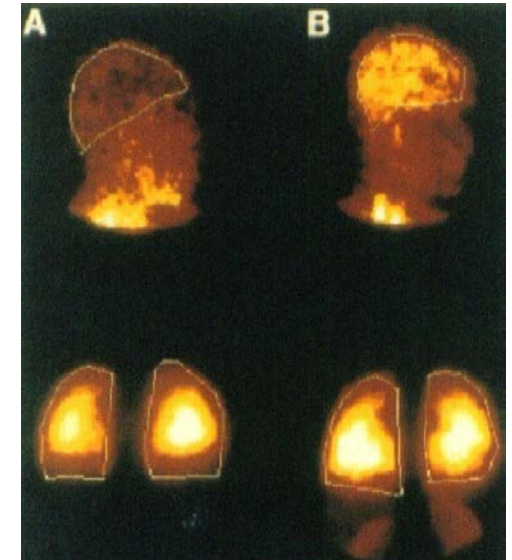


50%

Abnormal ABGs

HPS

MAA scan



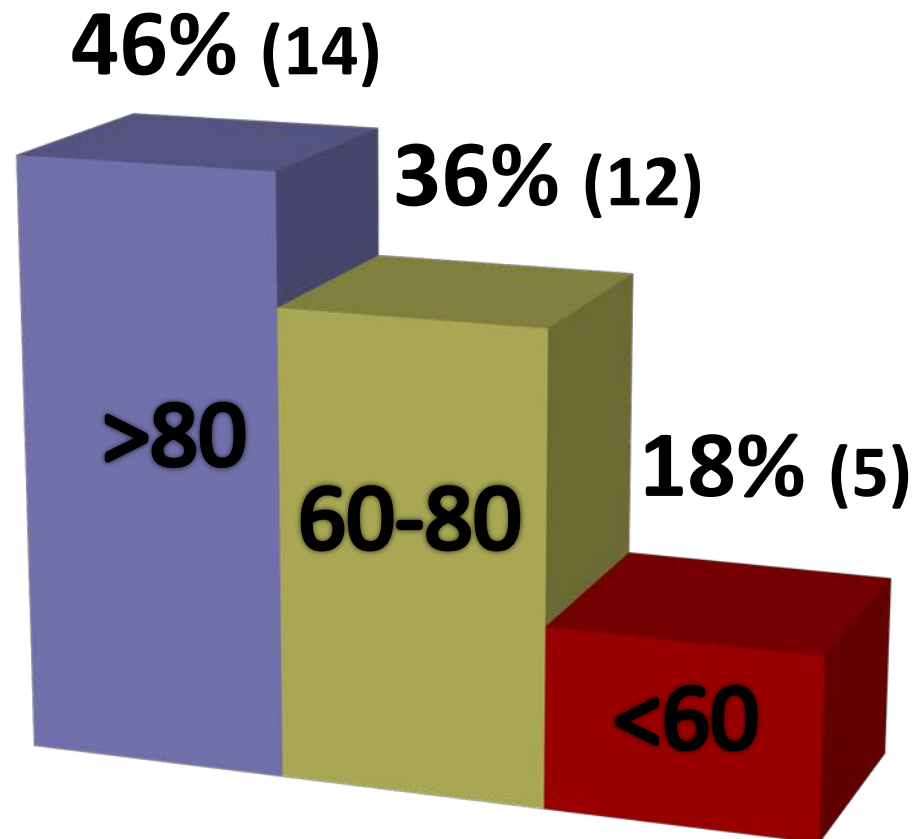
Quantitative
Standardization

PaO₂ in HPS at LT evaluation

(31% of patients had HPS)



UAB
Columbia
Mayo Clinic
UNC
U. Colorado
Tufts-NEMC



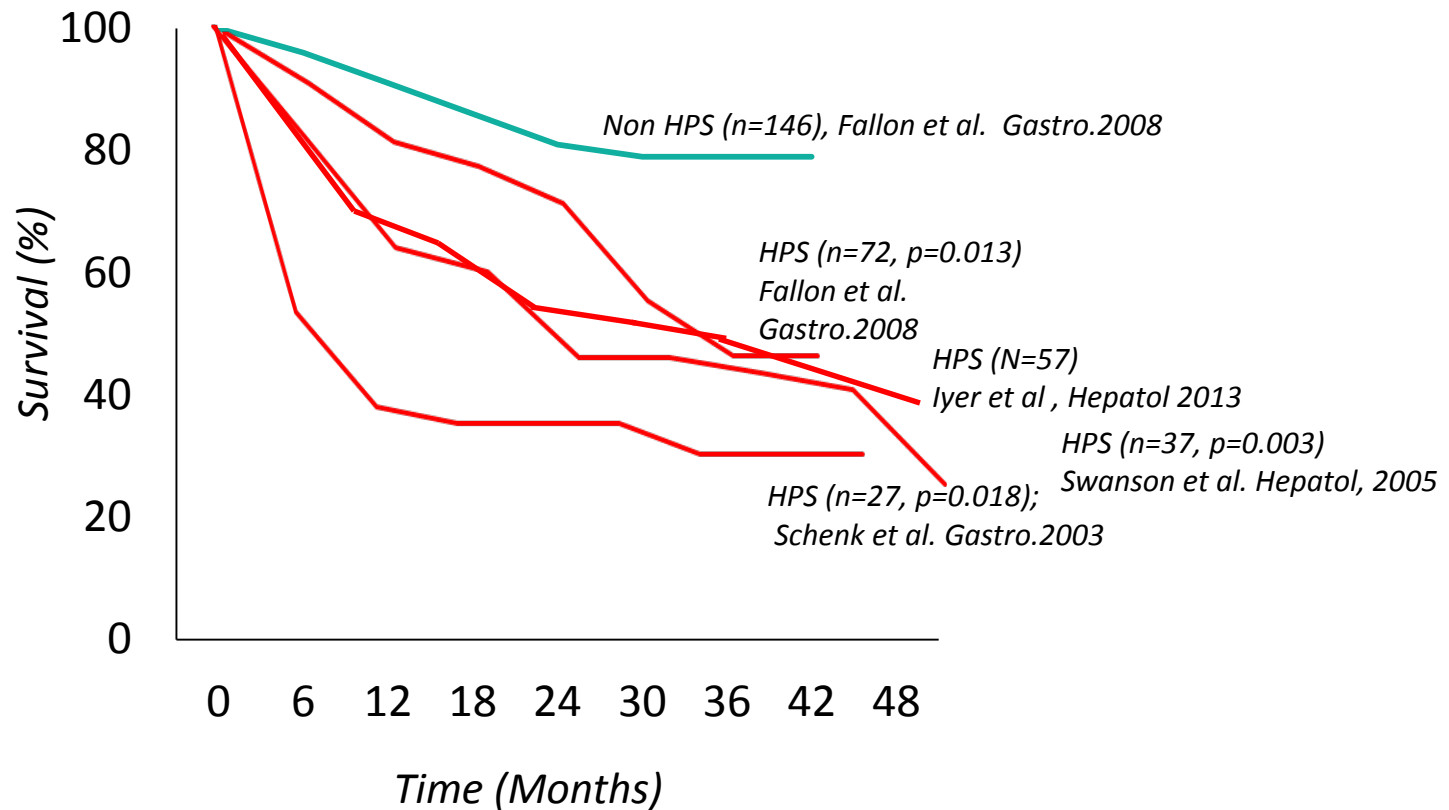
Clinical and demographic features

	HPS (n=72)	No HPS (n=146)	p
Age(years)	52±9	53±10	.86
Female sex, n(%)	30 (42)	53 (36)	.44
Race/ethnicity, n(%)			
Non-Hispanic white	65 (90)	110 (75)	.03
Hispanic white	3 (4)	18 (12)	
Non-Hispanic black	1 (1)	12 (8)	
Etiology of liver disease, n(%)			
Alcohol	28 (39)	60 (41)	.76
Hepatitis C infection	33 (46)	67 (46)	.99
HBV	1 (1)	9 (6)	.17
Cryptogenic / NAFLD	14 (19)	25 (17)	.67
AIH/ PSC/PBC	8 (11)	21 (14)	.50

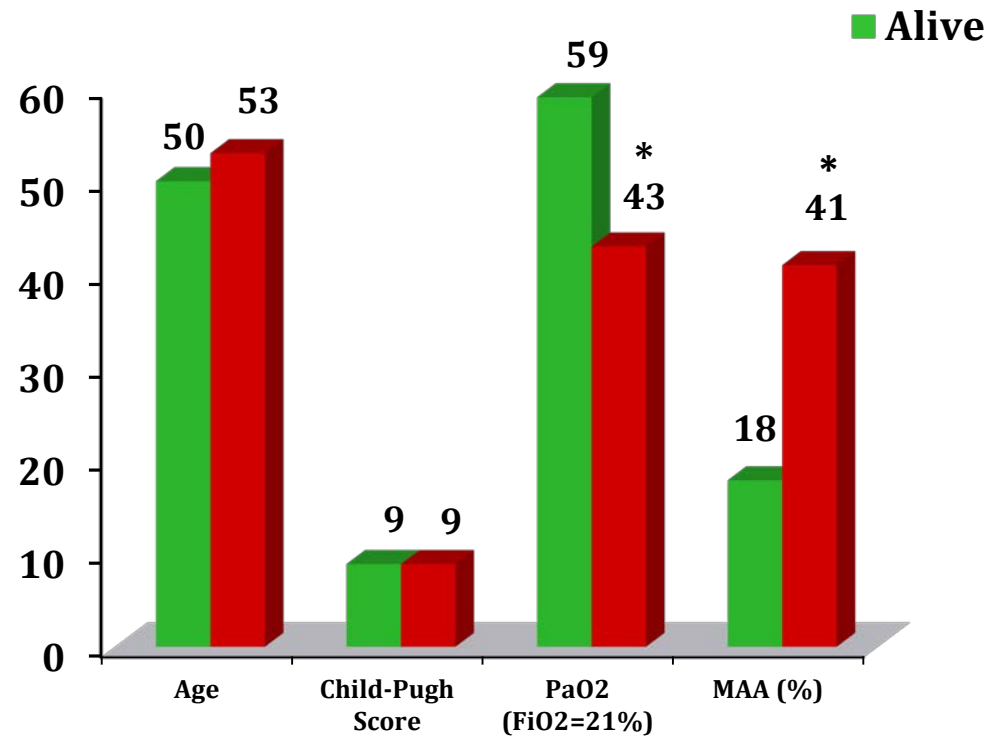
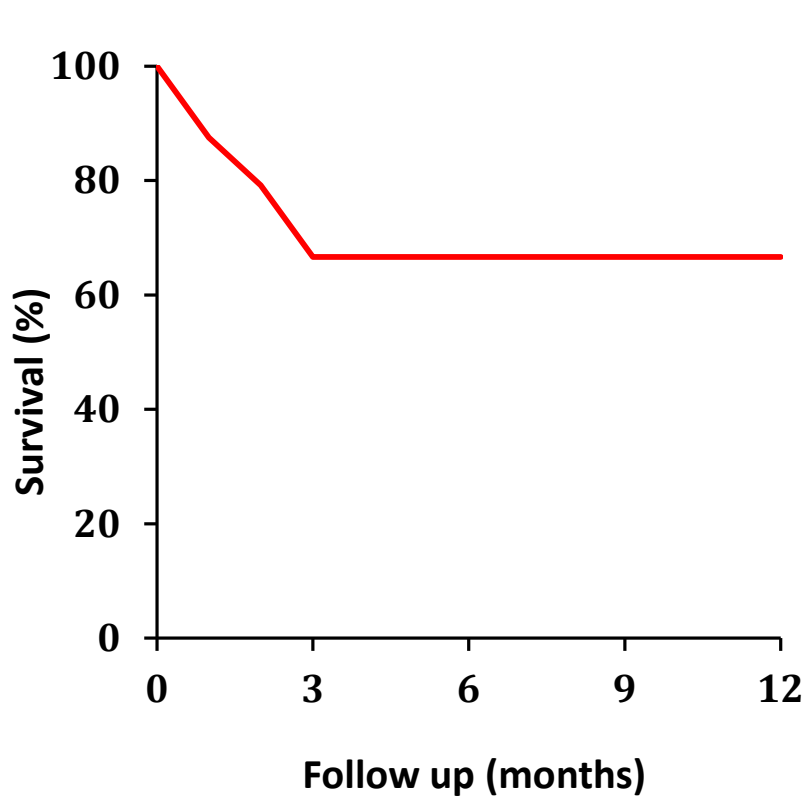
Clinical and demographic features

	HPS (n=72)	No HPS (n=146)	p
MELD score	13 ± 4	13 ± 5	.76
Complications n(%)			
Ascites	40 (56)	78 (53)	.77
Variceal bleeding	18 (25)	33 (23)	.69
Encephalopathy	33 (46)	66 (46)	.97
SBP	6 (8)	6 (4)	.22
HCC	5 (7)	14 (10)	.52
Hepatic Hydrothorax	4 (6)	4 (3)	.3
Past medical history n (%)			
TIPS	4 (6)	13 (9)	.39
Coronary Artery Disease	5 (7)	8 (6)	.68
Smoking	35 (49)	93 (64)	.03
Chronic Alcohol Use	43 (61)	104 (72)	.08

HPS: SURVIVAL



HPS FEATURES AND LT OUTCOME



HPS MELD Exception criteria

Initial Request

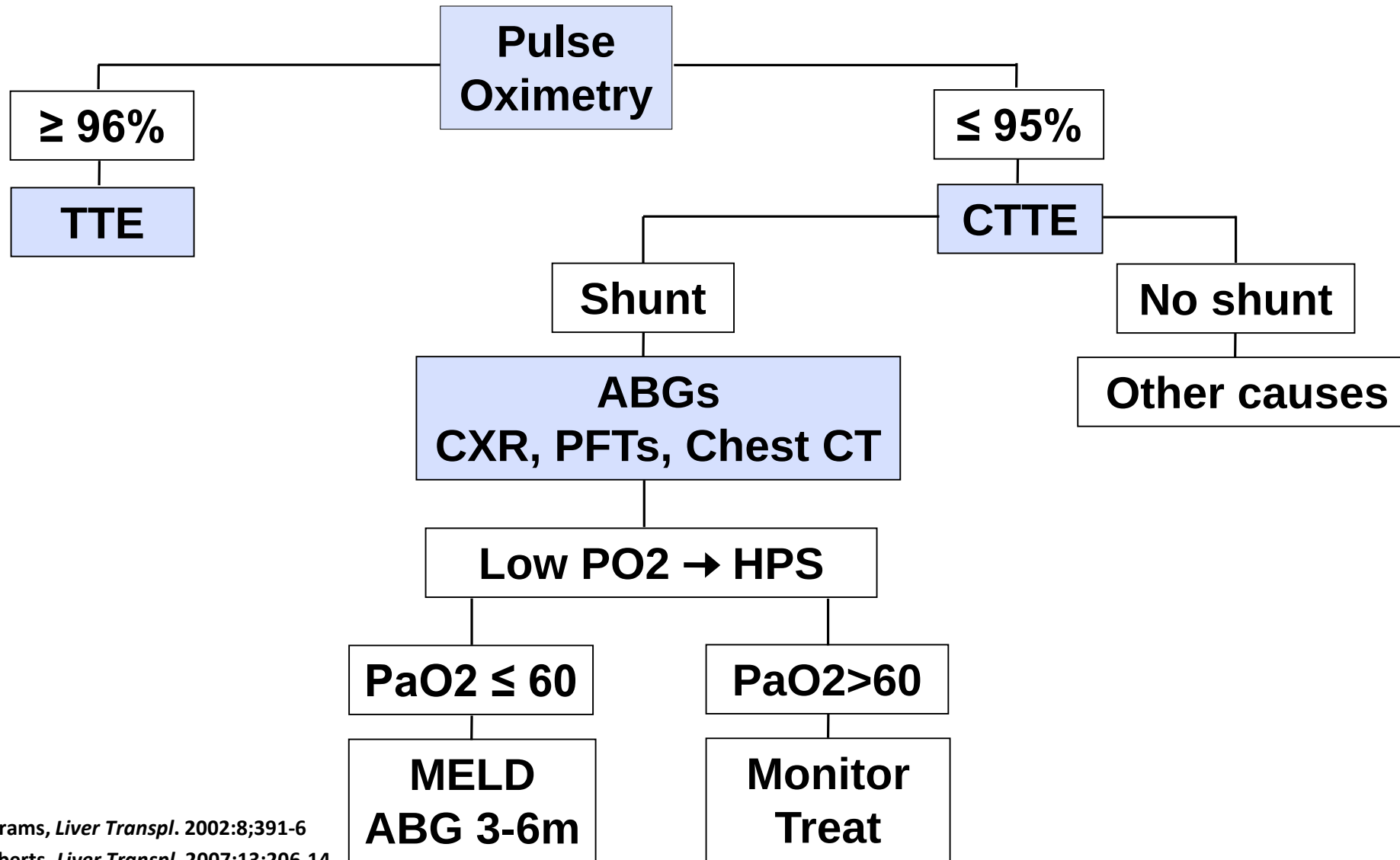
Clinical evidence of portal hypertension

- Evidence of a shunt by
 - contrast ECHO
 - Lung Scan
- PaO₂ < 60 mmHg (room air, at rest)
- No evidence of underlying primary pulmonary disease

Renewal Request (increase 3 points)

Resubmit above every 3 months

LT EVALUATION



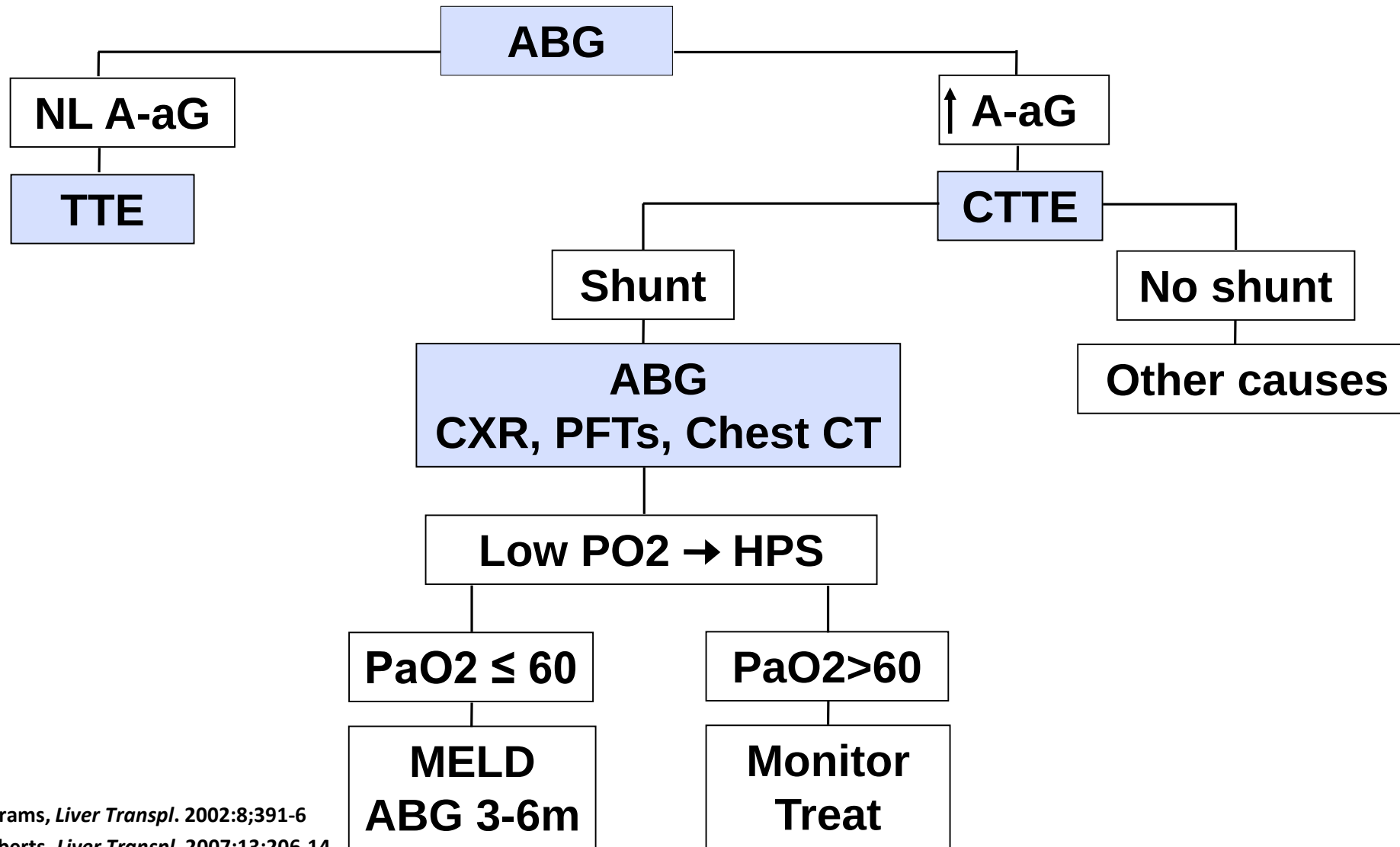
Abrams, *Liver Transpl.* 2002;8;391-6

Roberts, *Liver Transpl.* 2007;13:206-14

Arguedas, *Clin Gastro Hepatol.* 2007;5;749-54

Kochar, *Dig Dis Sci.* 2011;56;1862-8

LT EVALUATION



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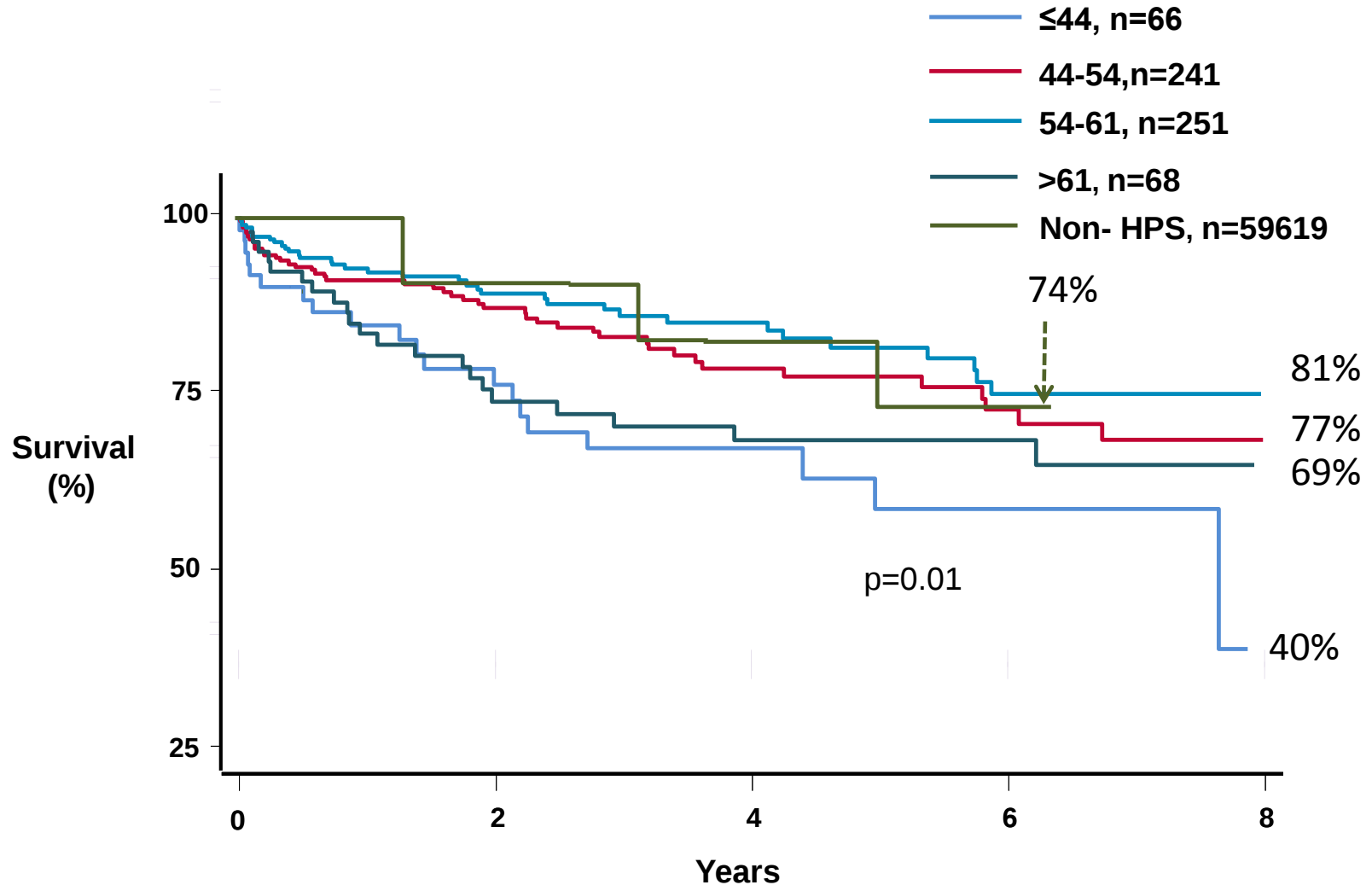
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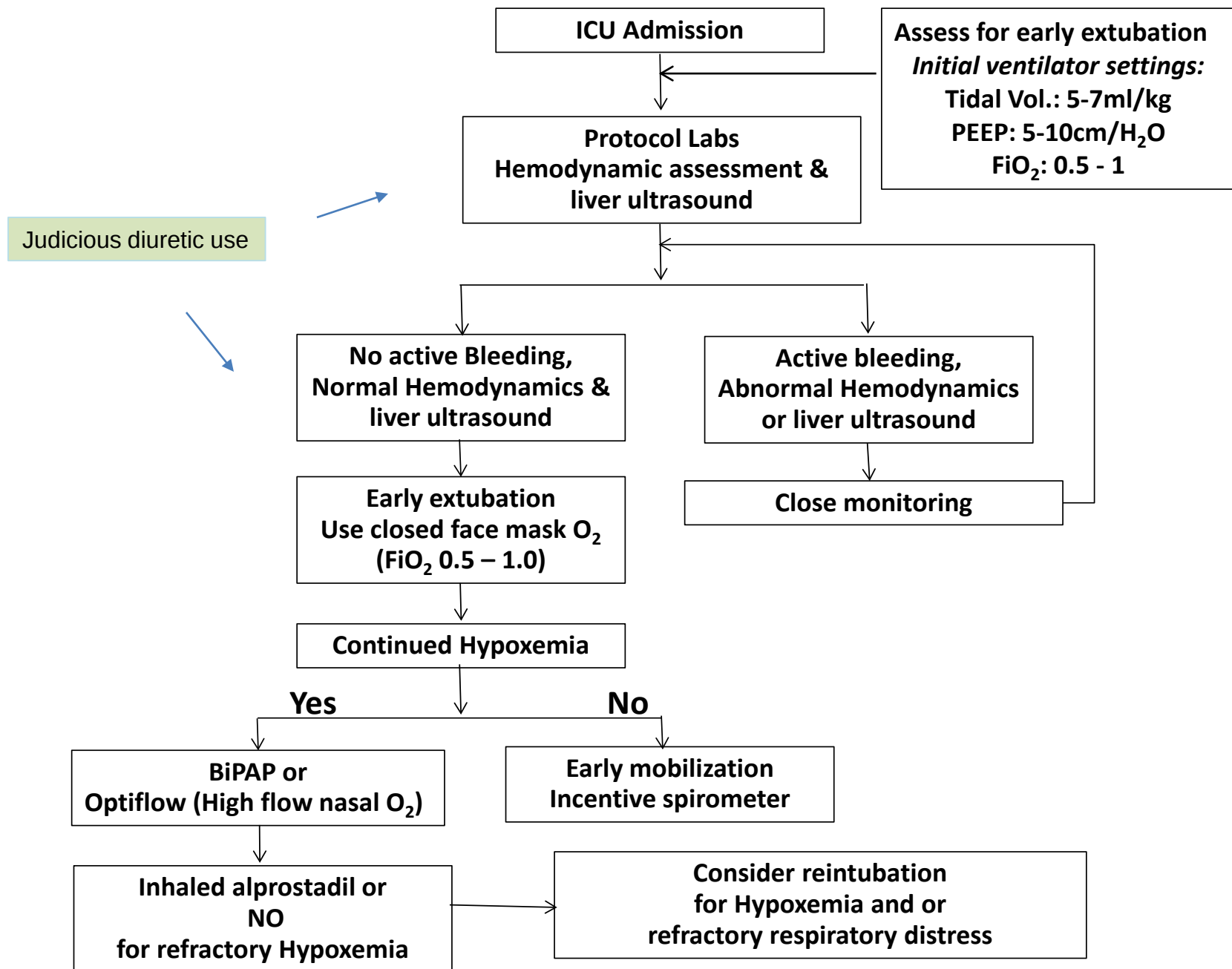
HPS: Post-OLT Survival

Study	Design	Sample Size	PaO ₂ mmHg	follow-up (months)	Survival
Arguedas (2003)	Prospective	24	54	12	71%
Taille (2003)	Retrospective	23	51	17	69%
Schenk (2003)	Prospective	7	68		58%
Swanson (2005)	Retrospective	24	57	60	79%
Schiffer (2006)	Prospective	9	60	6	67%
Deberaldini (2008)	Retrospective	25	77	49	60%
Gupta (2009)	Retrospective	21	50	20	95%
Iyer (2013)	Retrospective	28		39	88%
Goldberg (2014)	Retrospective	631		60	76%

HPS: Waitlist Outcomes

HPS Post-LT Survival





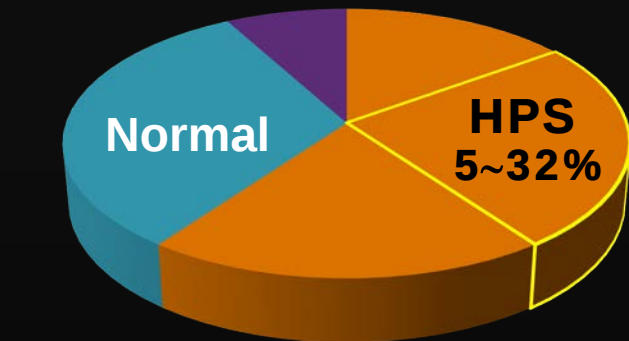
Overview of HPS

Yang et al. AASLD 2015

Liver disease

Constriction

Dilation



Pulmonary microvasculature

- Pulmonary vasodilation
- Angiogenesis

PERFUSION

- Surfactant protein reductions
- AT2 cell apoptosis

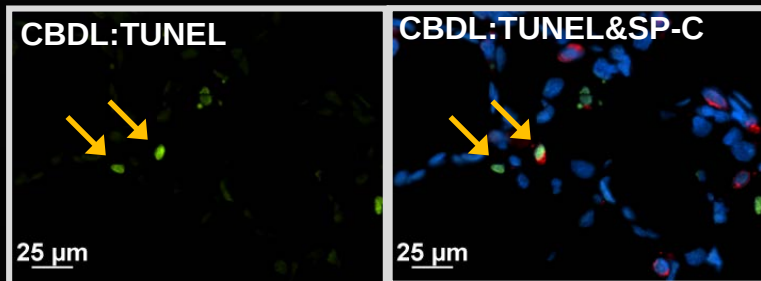
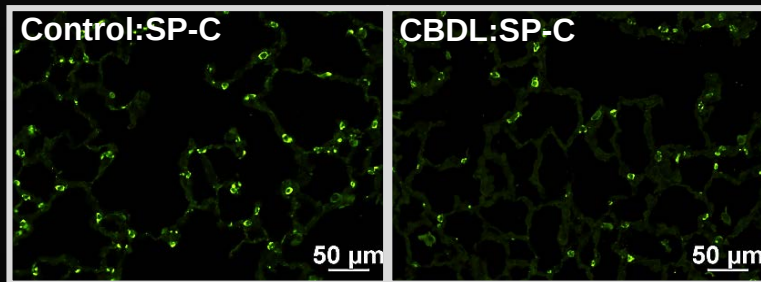
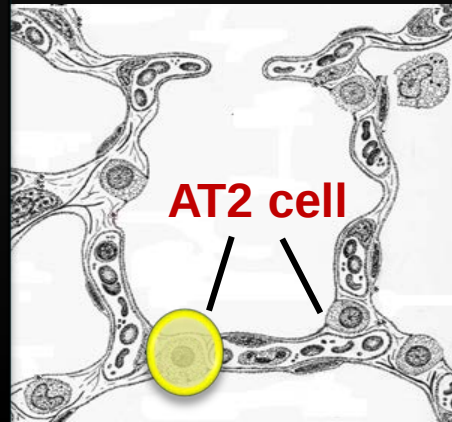
VENTILATION

Abnormal gas exchange ($AaPO_2 \uparrow$ / $PO_2 \downarrow$)

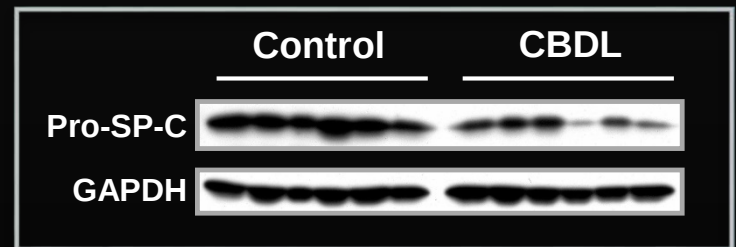
Hepatopulmonary syndrome (HPS)

AT2 cell alterations in experimental HPS

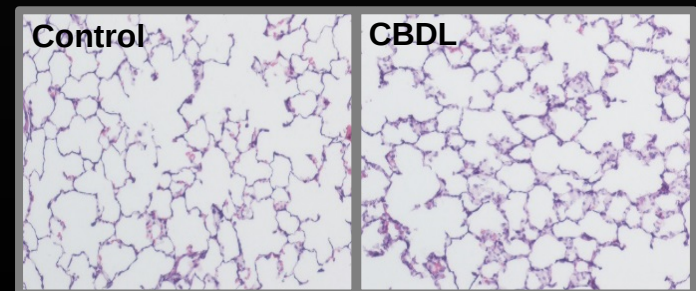
Common bile duct
ligation (CBDL)



AT2 cell apoptosis



SP reduction



Alveolar airspace (Lm) decrease



Sorafenib in Hepatopulmonary Syndrome

Sorafenib in HPS (SHPS) is a double blinded, parallel armed, placebo controlled, phase-II randomized control trial studying the efficacy of Sorafenib in improving gas exchange, functional status and quality of life among hepatopulmonary syndrome (HPS) patients.

Sorafenib is multi-specific receptor tyrosine kinase inhibitor targeting the vascular endothelial factor receptor-2 to inhibit neo-angiogenesis, as observed in experimental models of HPS.

The study target for enrollment is 50 patients at four centers –University of Texas-Houston, TX; Mayo Clinic, Rochester, MN; Columbia University Medical Center, New York, NY And University of Pennsylvania Health System, Philadelphia, PA.

HPS: ITLS *Treatment* Guidelines

- *Supplemental oxygen :*
 - *Severe HPS*
 - *desaturation with exercise or sleep*
 - *Maintain $spO_2 \geq 90\%$*
(at Rest, Sleep or Exercise)
- *Garlic extracts: $PaO_2 \uparrow 10\text{mmHg}$*
(40% treated patients)
- *Liver Transplantation: Recommends modification of*
current MELD exception
(Room air $PaO_2 \leq 55\text{mmHg}$)

HEPATOPULMONARY SYNDROME (HPS)

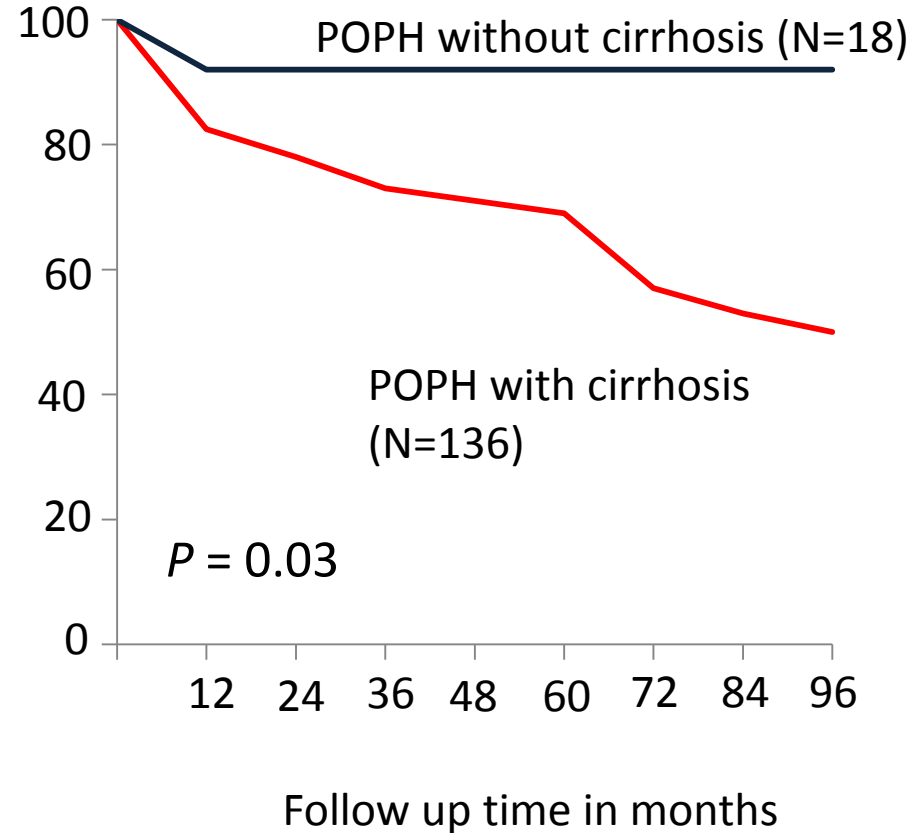
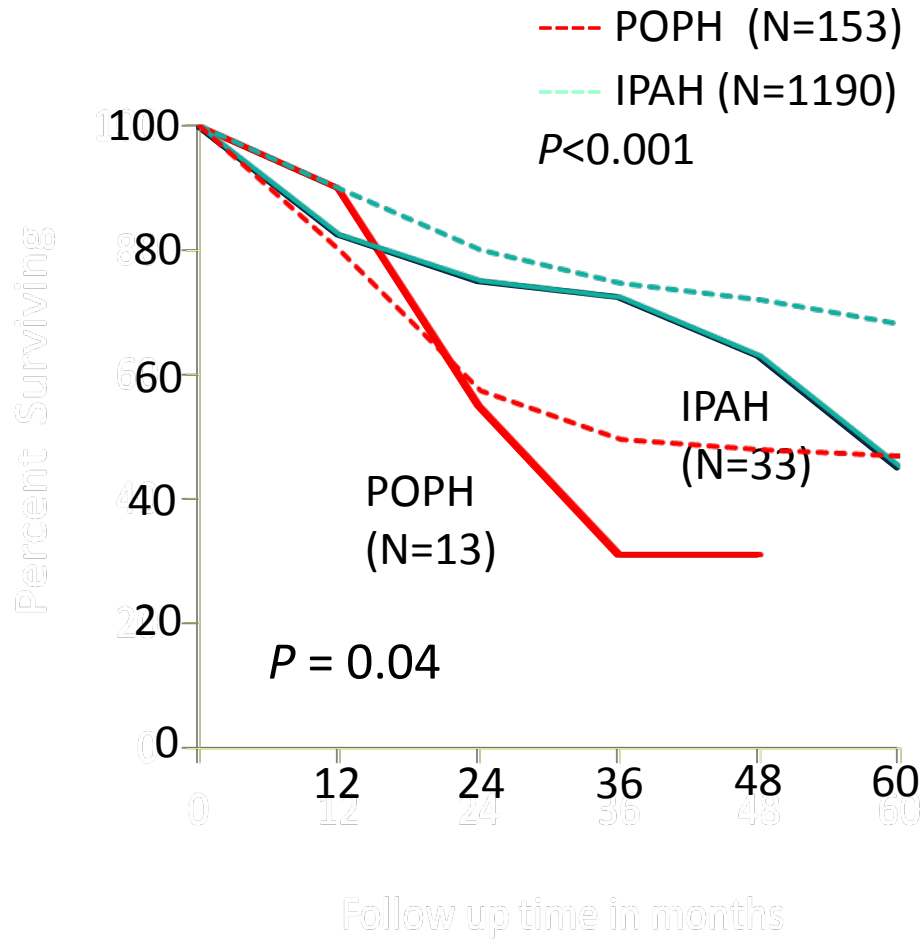
- **Common finding in cirrhosis**
- **Survival effects not fully defined**
- **Data for MELD exception and outcome of low quality**
- **Who should we not transplant?**
- **Medical therapies a key focus for current and future studies**

PORTOPULMONARY HYPERTENSION (POPH)

PORTOPULMONARY HYPERTENSION (POPH): DEFINITION

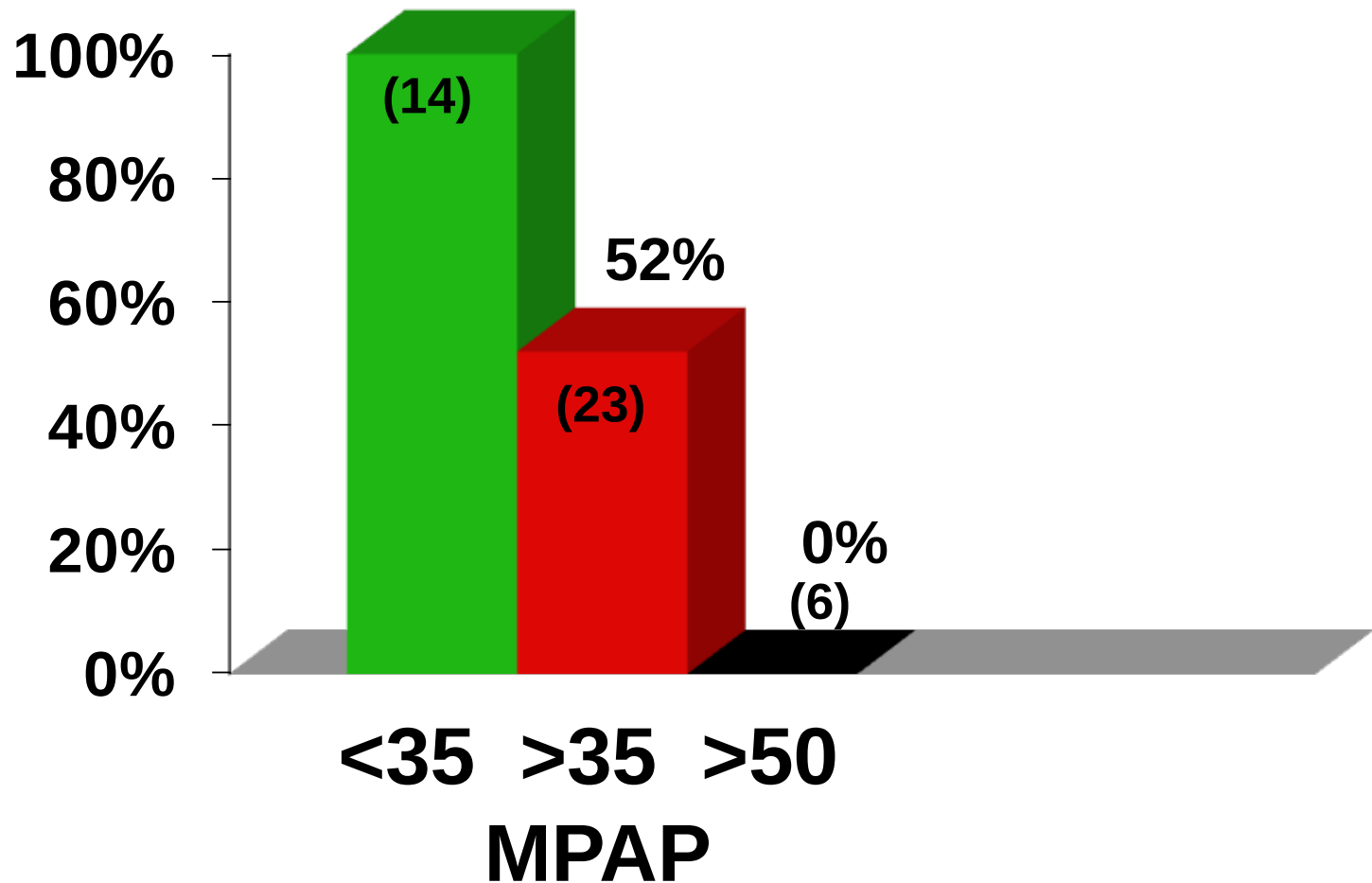
- **Portal hypertension**
- **Mean pulmonary artery pressure: >25 mmHg**
- **Pulmonary capillary wedge pressure: NL**
- **PVR > 240 dynes/sec/cm⁵**

POPH: NATURAL HISTORY



POPH: LIVER TRANSPLANTATION SURVIVAL

(n = 43)



LT EVALUATION

AASLD Practice Guidelines

Pre TIPS

Pulm sx, edema

Transthoracic Echocardiography

RV systolic pressure (RVSP)
Pulmonary artery systolic pressure (PASP)
> 40-50 mm Hg

Systolic estimate

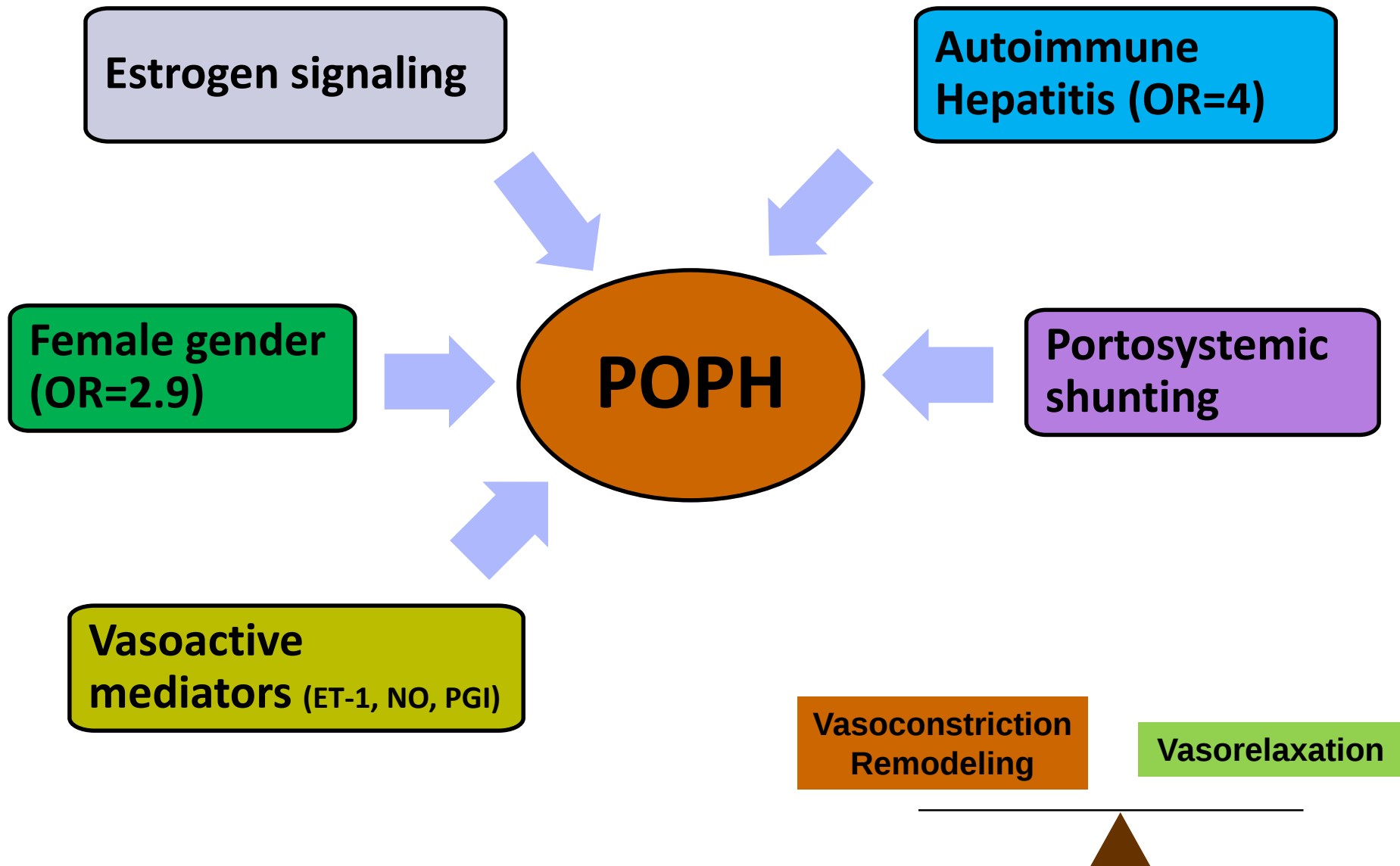
Right Heart
Catheterization (RHC)

Mean measured

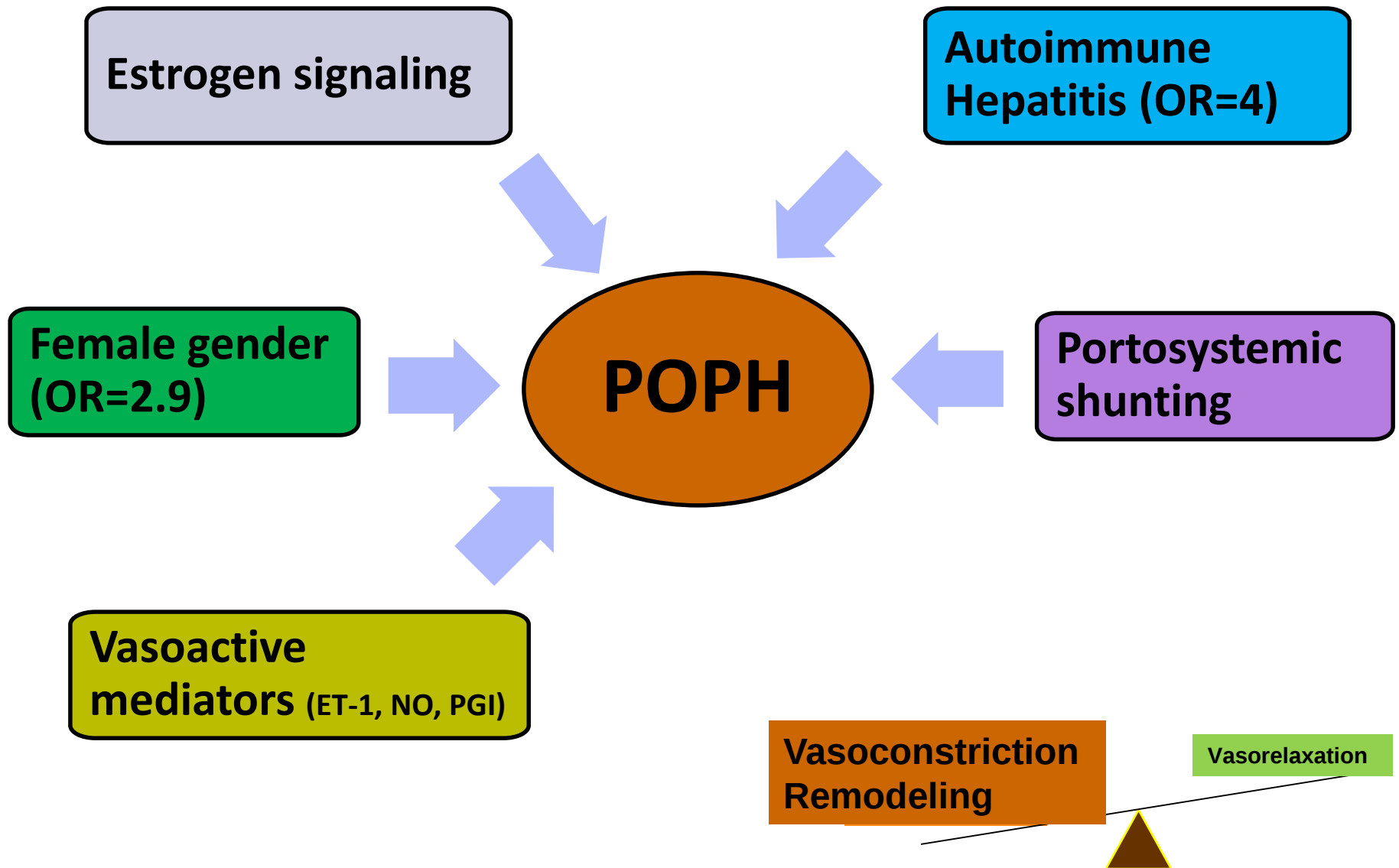
RHC in Cirrhosis

	mPAP	CI	PVR	PCWP
Hyperdynamic (25%)			NL	NL / 
Volume (25%)			NL	
POPH (50%)				NL

POPH: PATHOGENESIS

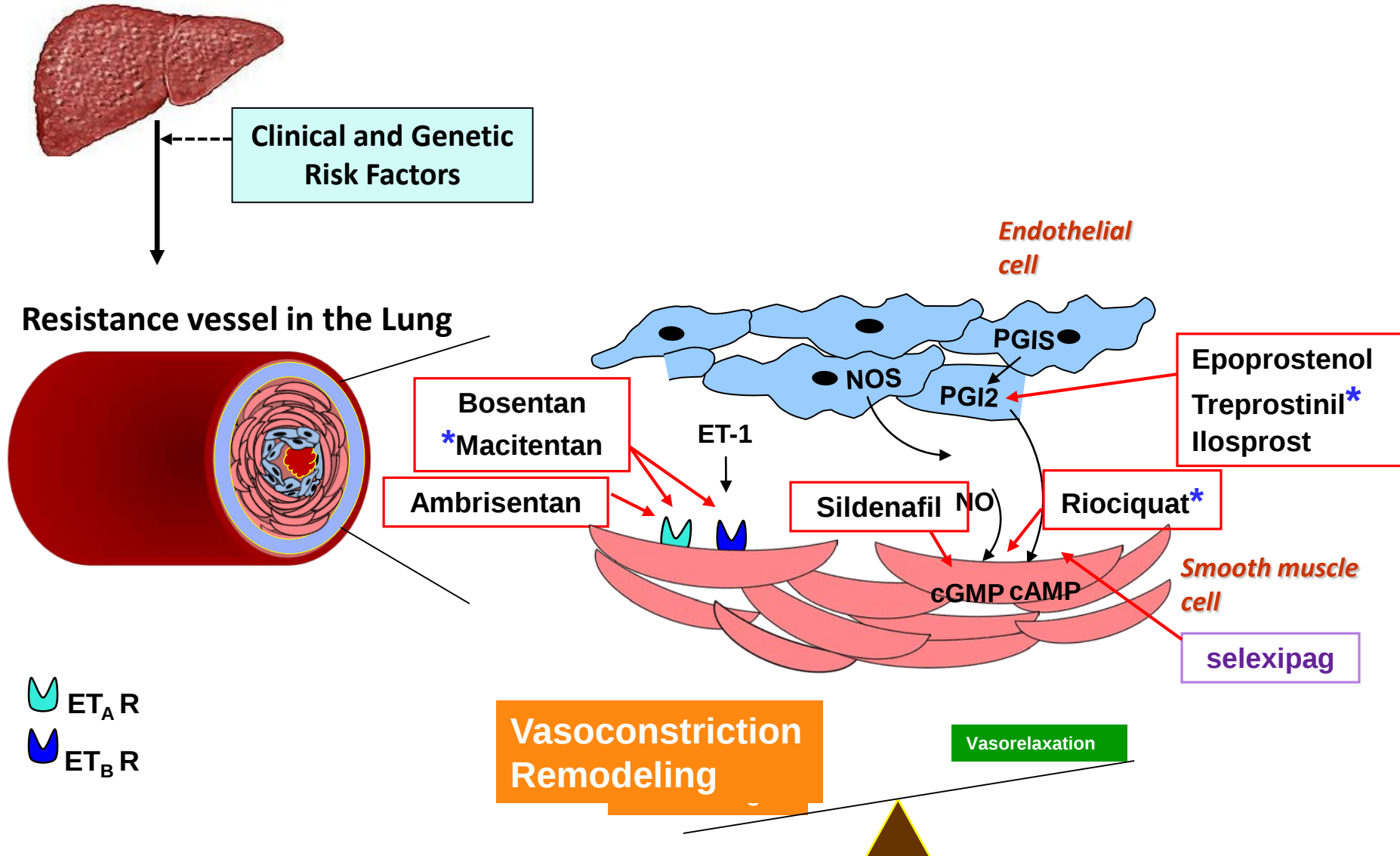


POPH: PATHOGENESIS



Cirrhosis
Portal Hypertension

PATHOGENESIS OF POPH



POPH MELD Exception criteria

Initial Request

- Abnormal Initial pulmonary hemodynamics
 - Mean pulmonary arterial pressure (MPAP) ≥ 35 mmHg
 - Pulmonary vascular resistance (PVR) ≥ 5 Woods
- Documentation of treatment
 - Flolan
 - Sildenafil
 - Ambersantin
 - other (specify)
- Post-treatment
 - MPAP < 35 mmHg
 - PVR < 400 dynes/sec/cm-5
 - Transpulmonary gradient > 12 mmHg

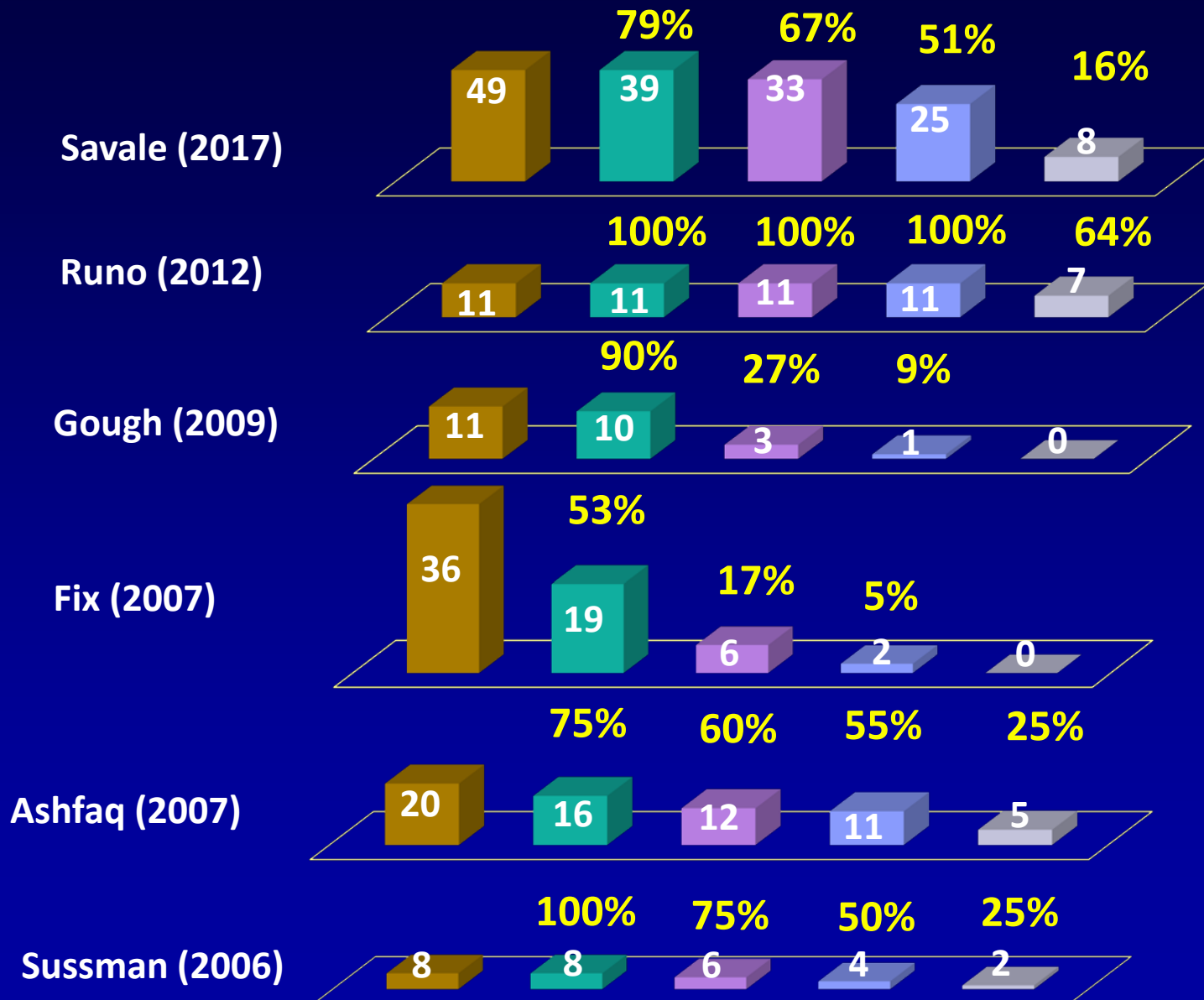
gradient _____ date _____

Renewal Request (increase 3 points)

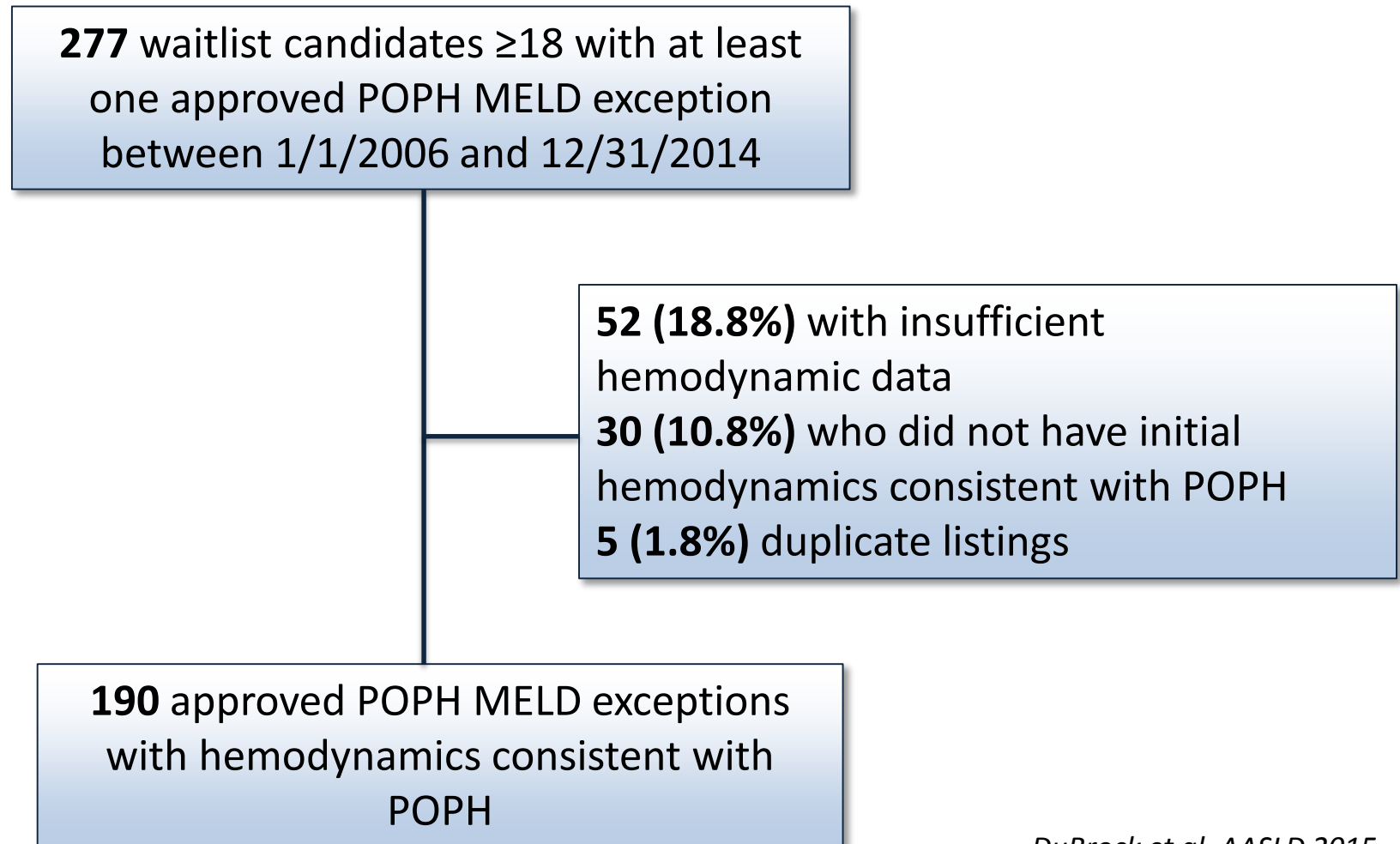
MPAP < 35 mmHg (confirmed by repeat heart catheterization)

POPH: REVERSAL WITH OLT?

mPAP>35 Therapy mPAP<35 OLT Off therapy



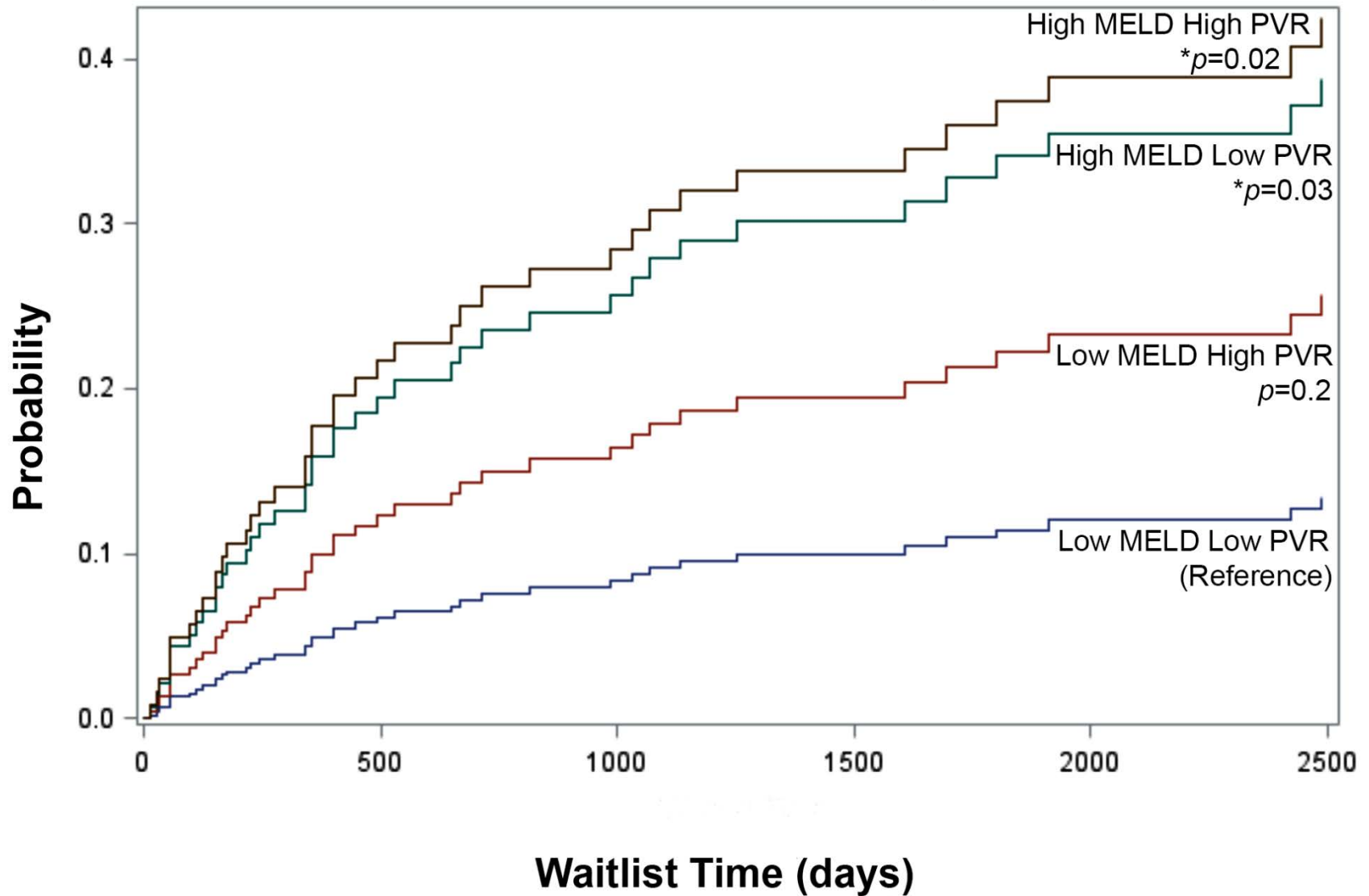
Predictors of Waitlist Mortality in Patients with POPH: An Analysis of the UNOS Database



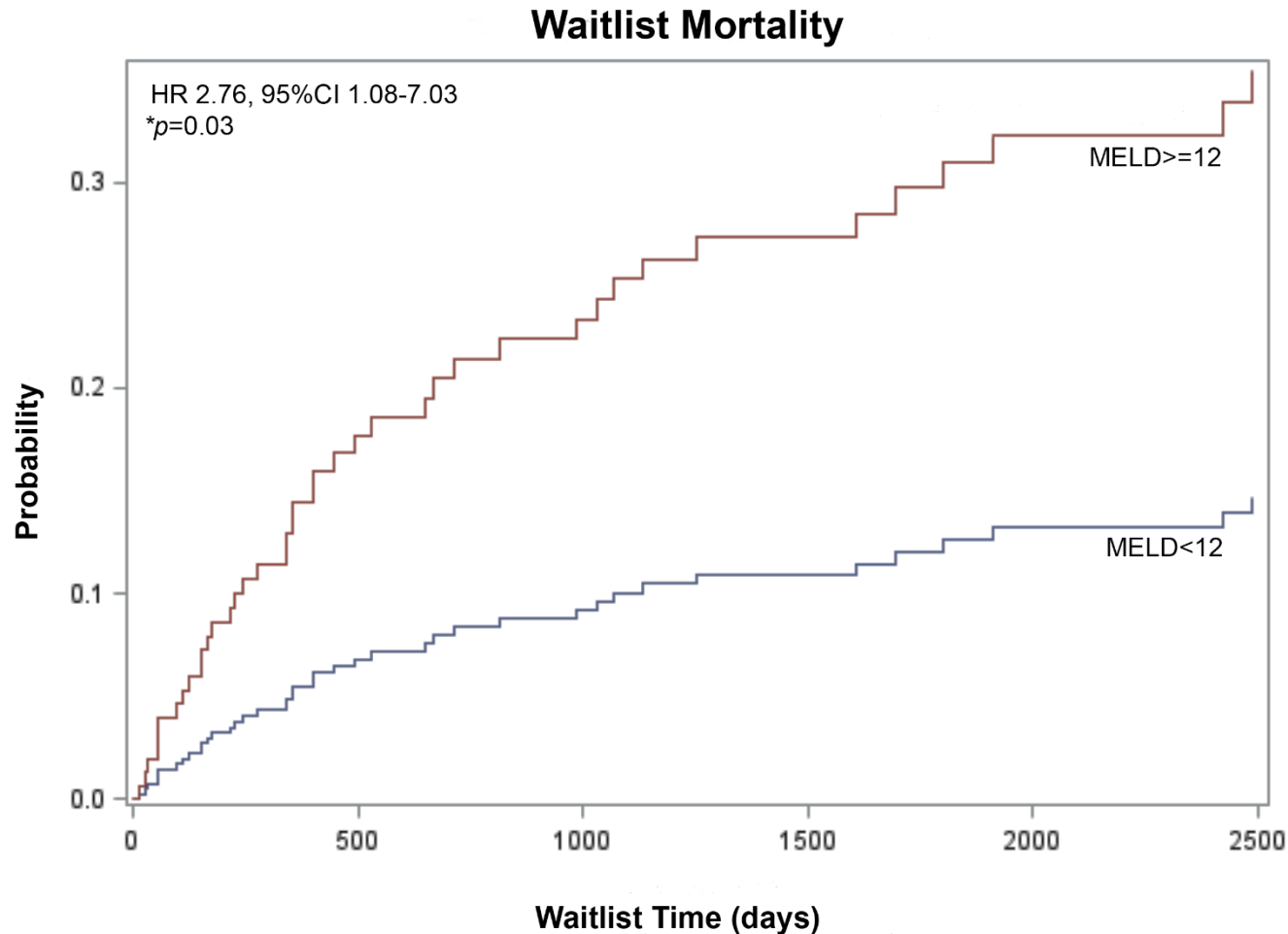
Predictors of Waitlist Mortality

Variable	Univariate Model		Bivariate Model	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Age at listing	1.02 (0.98-1.06)	0.3		
Female gender	1.29 (0.72-2.3)	0.4		
Initial Native MELD	1.12 (1.07-1.18)	<0.001	1.14 (1.08-1.19)	<0.001
Complications of Liver Disease				
Ascites	1.49 (0.76-2.93)	0.3		
Encephalopathy	1.12 (0.61-2.05)	0.7		
Initial Hemodynamics				
mPAP, mmHg	1.00 (0.96-1.04)	1.0		
PVR, per 100 dynes	1.05 (0.95-1.16)	0.35	1.11 (1.01-1.22)	0.03
CO, L/min	0.90 (0.66-1.23)	0.51		

Waitlist Mortality



A minimum MELD for POPH exceptions?



MELD 12: 93.6% NPV for predicting 1 year waitlist mortality

Patients with MELD < 12 received 25% of liver transplants

DuBrock et al. AASLD 2015

PORTOPULMONARY HYPERTENSION (POPH)

- **Accurate phenotyping is critical**
- **Survival effects not fully defined**
- **Data for LT outcomes preliminary**
- **Who should we transplant?**