

Biomarkers of PSC

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Biomarkers of PSC Currently Used in Clinical Practice

Biomarkers Used in Prognostic Models of PSC

Wiesner <i>et al</i> , 1989	Age	Bilirubin	Biopsy	IBD	Hemoglobin
Farrant <i>et al</i> , 1991	Age	Alk Phos	Biopsy	Splenomegaly	Hepatomegaly
Dickson <i>et al</i> , 1992	Age	Bilirubin	Biopsy	Splenomegaly	
Broome <i>et al</i> , 1996	Age	Bilirubin	Biopsy		
Okolicanyi <i>et al</i> , 1996		Cholesterol	AST	Albumin	Hemoglobin
Kim <i>et al</i> , 2000	Age	Bilirubin	AST	Albumin	Variceal Bleed

“A Revised Natural History Model for Primary Sclerosing Cholangitis”

Kim, WR, Therneau, TM, Wiesner, RH, Poterucha, JJ, Benson, JT, Malinchoc, M, LaRusso, NF, **Lindor, KD** and Dickson, ER.

Mayo Clinic Proceedings 2000; 75: 688-694.

Risk Score =

$$\begin{aligned}
 & 0.03 \times \text{Age (years)} \\
 & + 0.54 \times \text{Log}_e (\text{total Bilirubin [mg/dL]}) \\
 & - 0.84 \times \text{Albumin (g/dL)} \\
 & + 0.54 \times \text{Log}_e (\text{AST [IU/L]}) \\
 & + 1.24 \times \text{Variceal bleed (yes = 1; no = 0)}
 \end{aligned}$$

(typical scores range from -1 to 4, estimates survival up to 4 years out)

Biomarkers for the Prediction of Esophageal Varices in PSC Patients

Zein *et al*, 2000 Platelet Count Albumin Biopsy

“Prevalence and Predictors of Esophageal Varices in Patients with Primary Sclerosing Cholangitis”

Zein, CO, Lindor, KD and Angulo, P.

Hepatology 2004; 39: 204-210.

	Varices		Medium/Large Varices	
	Odds Ratio	(95% CI)	Odds Ratio	(95% CI)
Platelet count < 150 x 10 ³ /dL	14	(6.4 - 32.4)	13	(4.6 - 42.9)
Albumin < 3.3 g/dL	7.8	(3.8 - 16.7)	7.6	(2.7 - 24.8)
Biopsy (advanced stage: 3 - 4)	12.6	(5.1 - 38.4)	4.0	(1.4 - 14.7)

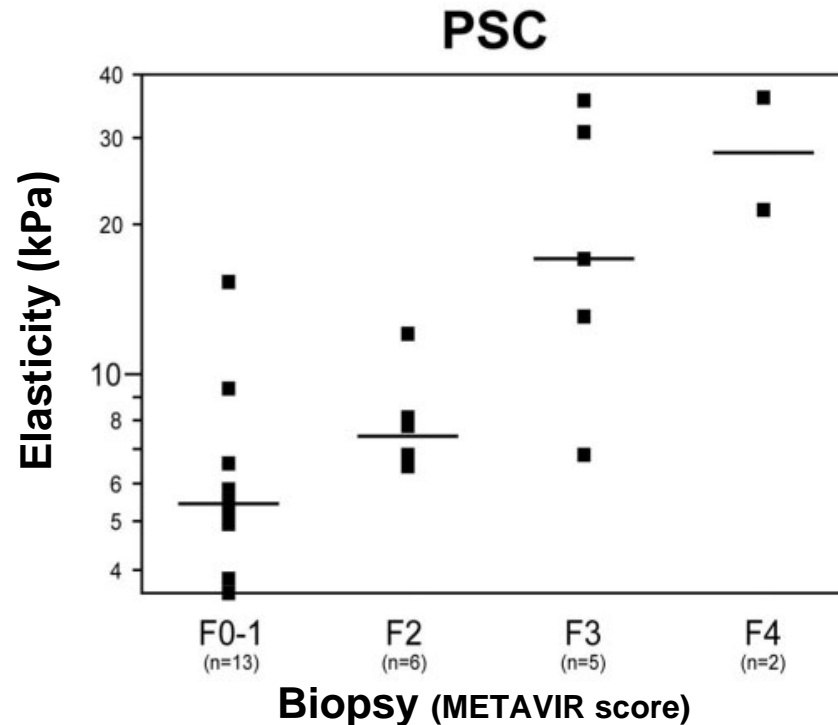
**New Biomarker
Technologies
Currently in
Clinical Trials**

FibroScan[®]: Transient Elastography

“Assessment of Biliary Fibrosis by Transient Elastography
in Patients with PBC and PSC”

Corpechot, C, El Naggar, A, Poujol-Robert, A, Ziol, M,
Wendum, D, Chazouilleres, O, de Ledinghen, V, Dhumeaux,
D, Marcellin, P, Beaugrand, M and Poupon, R

Hepatology 2006; 43: 1118-1124.

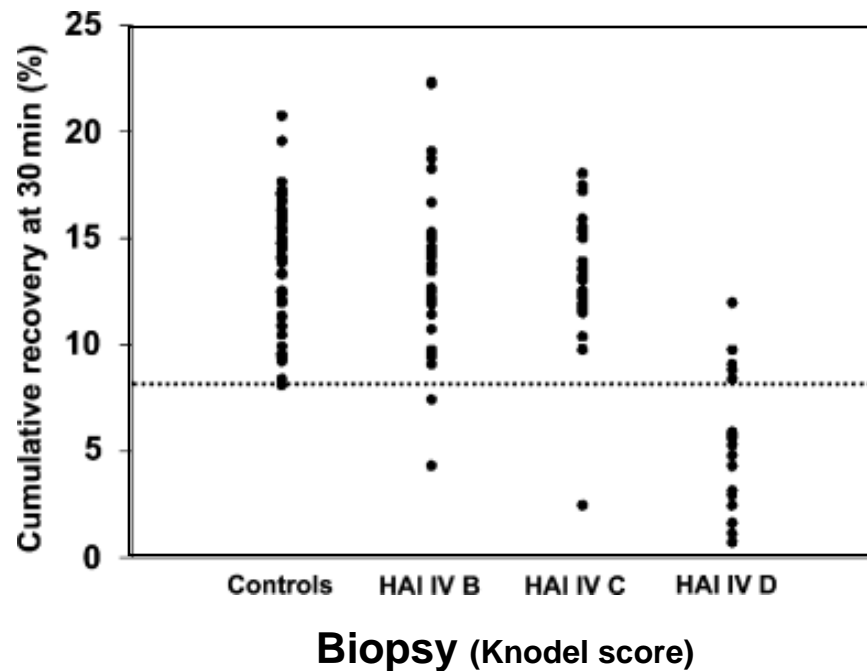


BreathID®: ¹³C-Methacetin Breath Test

“¹³C-Methacetin Breath Test as Liver Function Test in Patients with Chronic Hepatitis C Virus Infection”

Braden, B, Faust, D, Sarrazin, U, Zeuzem, S, Dietrich, CF, Caspary, WF and Sarrazin, C

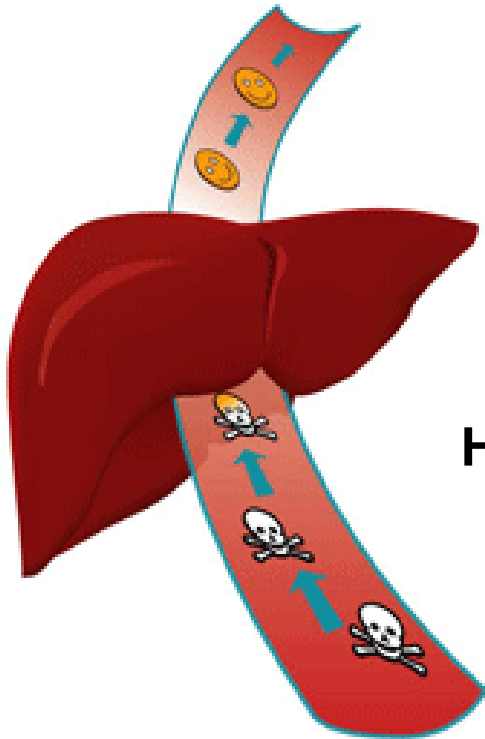
Alimentary Pharmacology and Therapeutics 2005; 21: 179-185



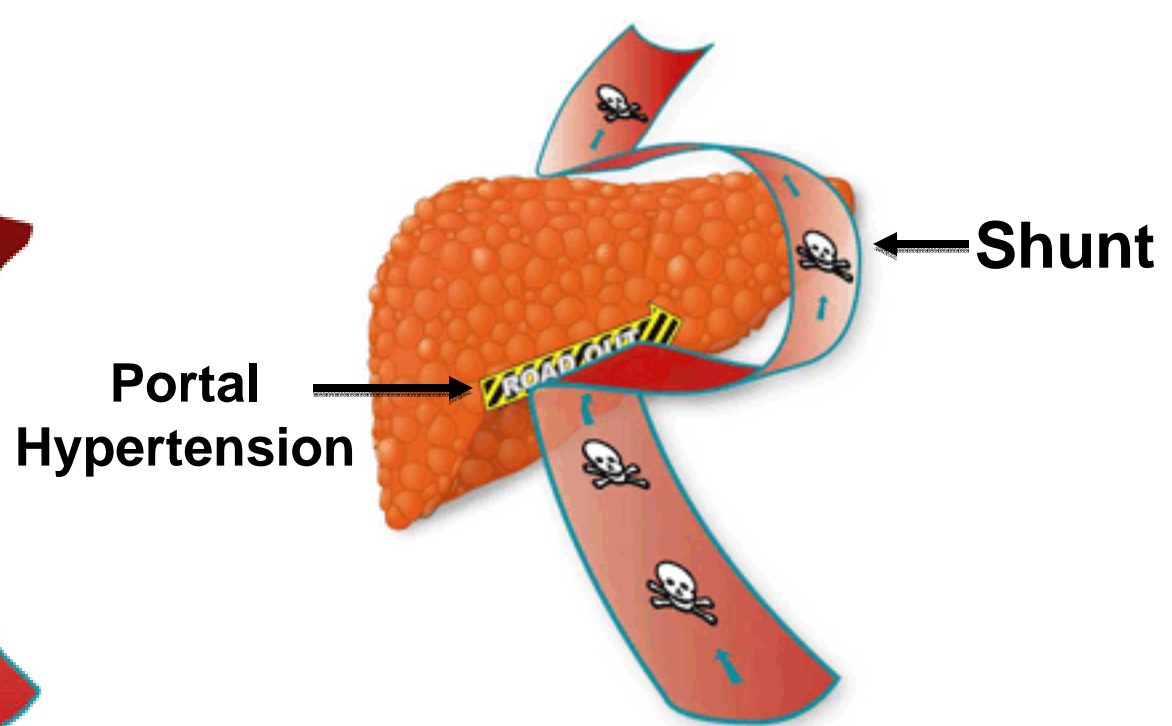
**A New Biomarker
Technology
Based on Assessment of
the Portal Circulation**

The Portal Circulation is Key in Assessing Liver Function

IN HEALTH

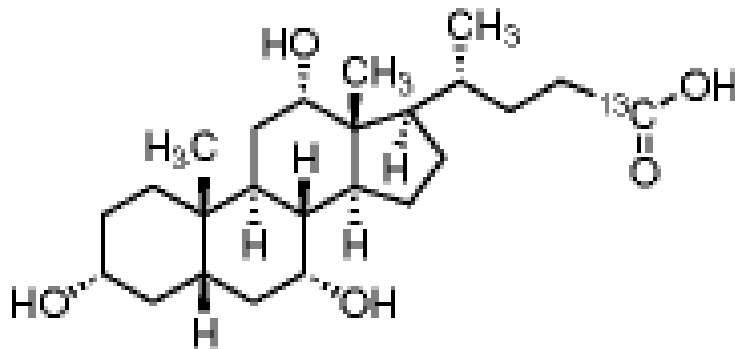


IN DISEASE



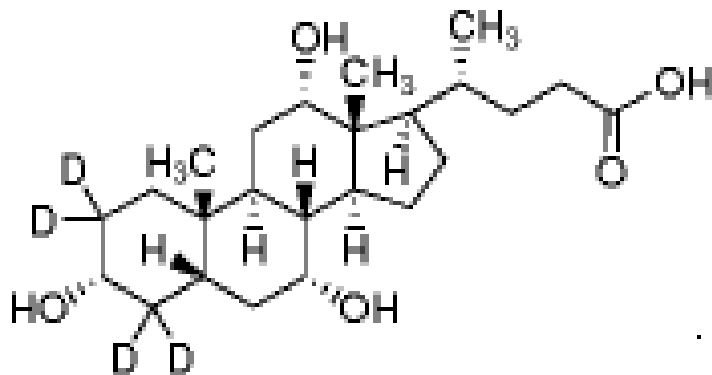
Stable Isotope Labeled Cholates Compounds for Liver Function Testing

[24-¹³C]-cholic acid (*m/z* 408)



Administered IV (20 mg)
measures clearance from
the systemic circulation

[2,2,4,4-²H]-cholic acid (*m/z* 411)



Administered Orally (40 mg)
measures clearance from
the portal circulation

Accuracy and Precision Statistics for Measuring Cholate Compounds in Human Serum

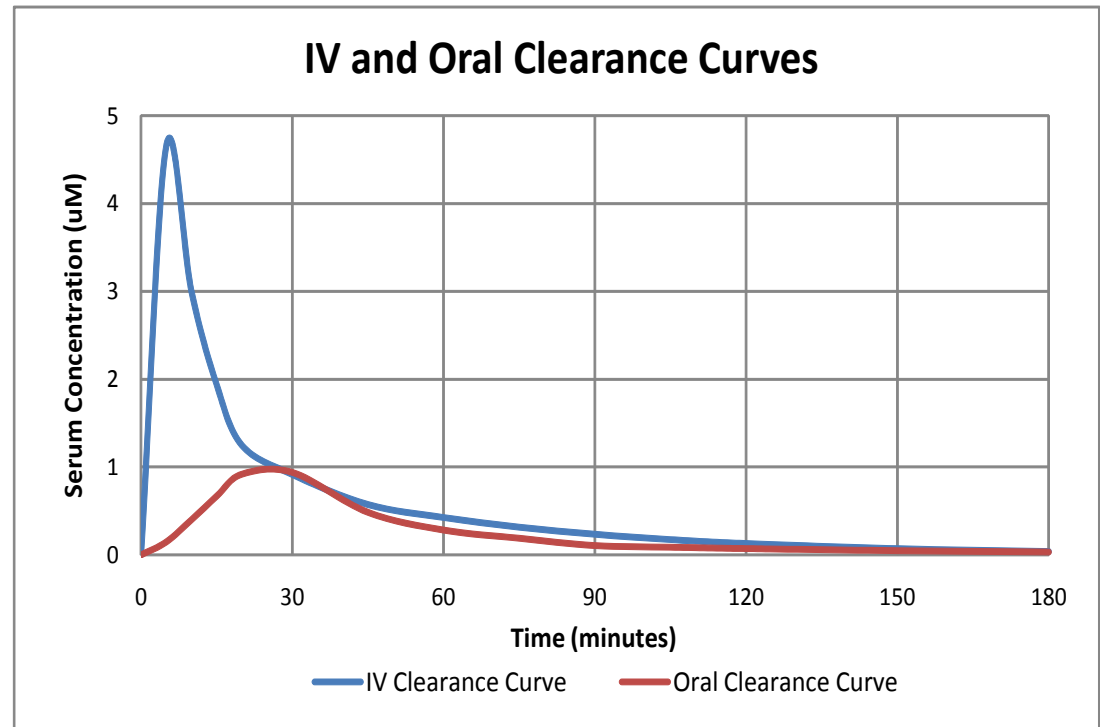
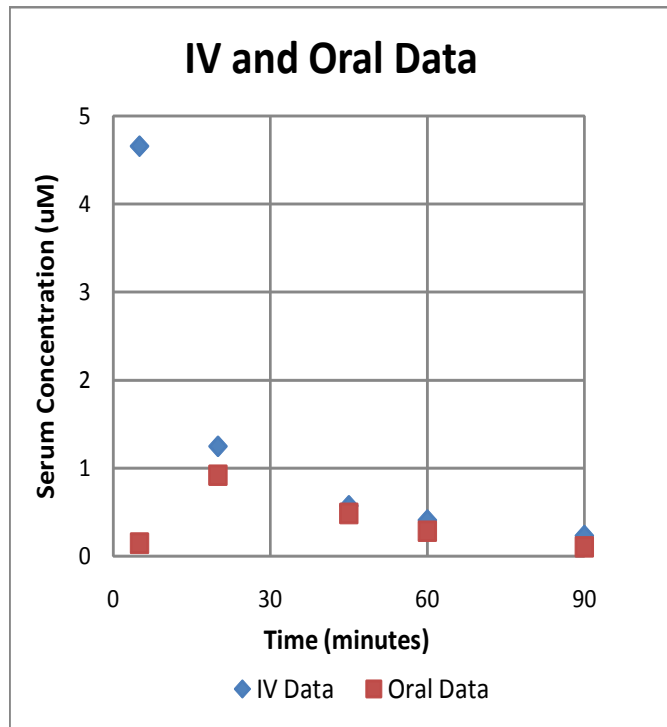
[24-¹³C]-cholic acid

Characteristic	Statistic	13C High	13C Medium	13C Low	13C LLOQ
		10.0 uM	2.0 uM	0.6 uM	0.1 uM
Accuracy	Mean Bias (%RE)	0.6	0.6	-1.0	2.8
Precision	Intrabatch (%CV)	0.9	1.4	2.9	10.5
	Interbatch (%CV)	2.3	2.4	3.7	12.2
Accuracy + Precision	Mean + Interbatch	2.9	3.0	4.7	14.9

[2,2,4,4-²H]-cholic acid

Characteristic	Statistic	4D High	4D Medium	4D Low	4D LLOQ
		5.0 uM	2.0 uM	0.5 uM	0.1 uM
Accuracy	Mean Bias (%RE)	0.2	-1.3	-1.1	0.1
Precision	Intrabatch (%CV)	1.0	1.2	1.2	2.6
	Interbatch (%CV)	1.6	1.9	2.0	3.9
Accuracy + Precision	Mean + Interbatch	1.8	3.1	3.1	4.0

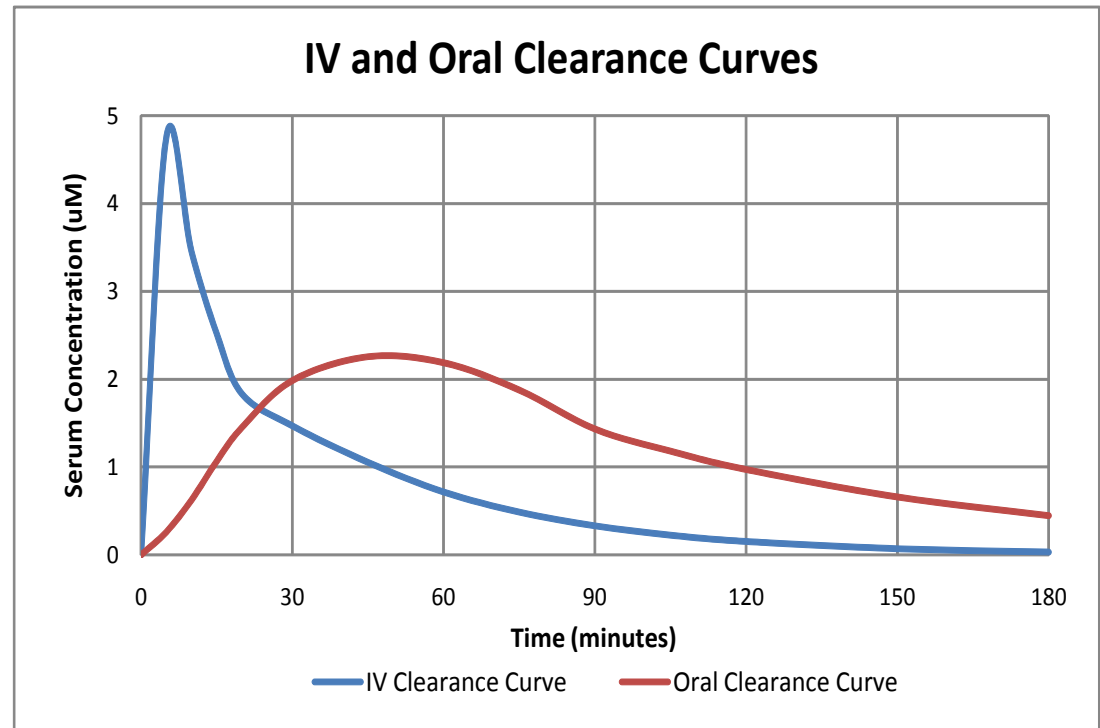
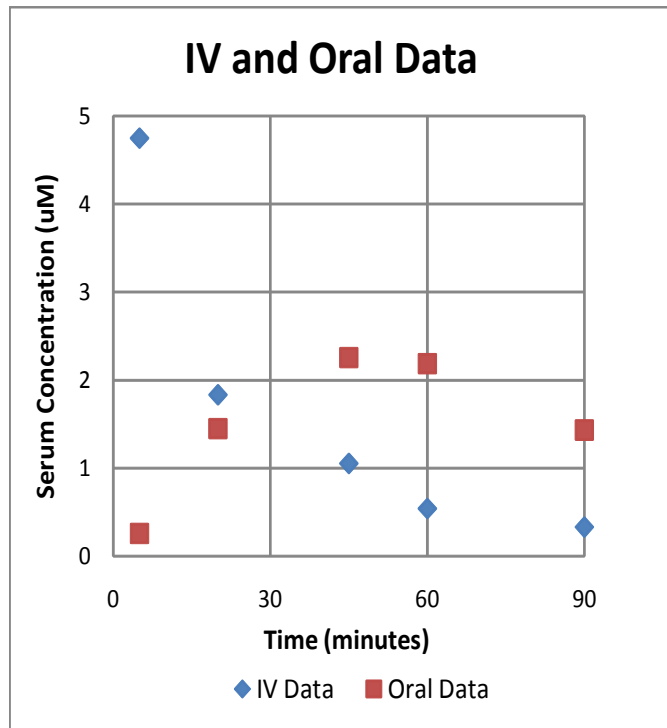
Cholate Clearances and Shunt in a Normal Healthy Control



Data from a Normal Healthy Individual

IV AUC (uM*min)	PO AUC (uM*min)	K Elim (min ⁻¹)	V Distrib (L/kg)	IV Clear (mL/min)	PO Clear (mL/min)	Shunt Fraction
117	46	0.088	0.112	361	2115	17.1%

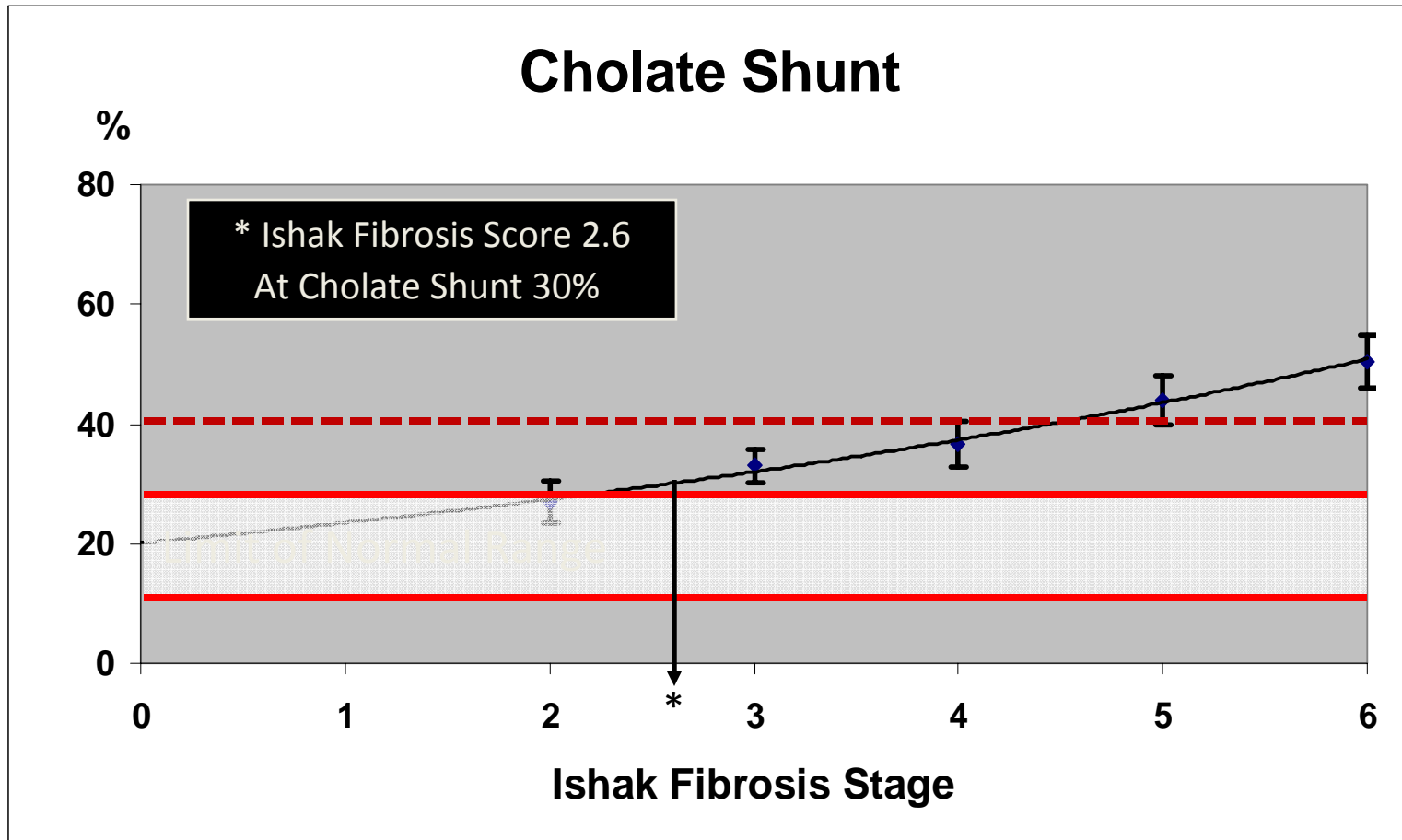
Cholate Clearances and Shunt in a HALT-C Patient



Data from a HALT-C Patient
 Ishak Fibrosis Score of 4
 Endoscopy revealed large esophageal varices

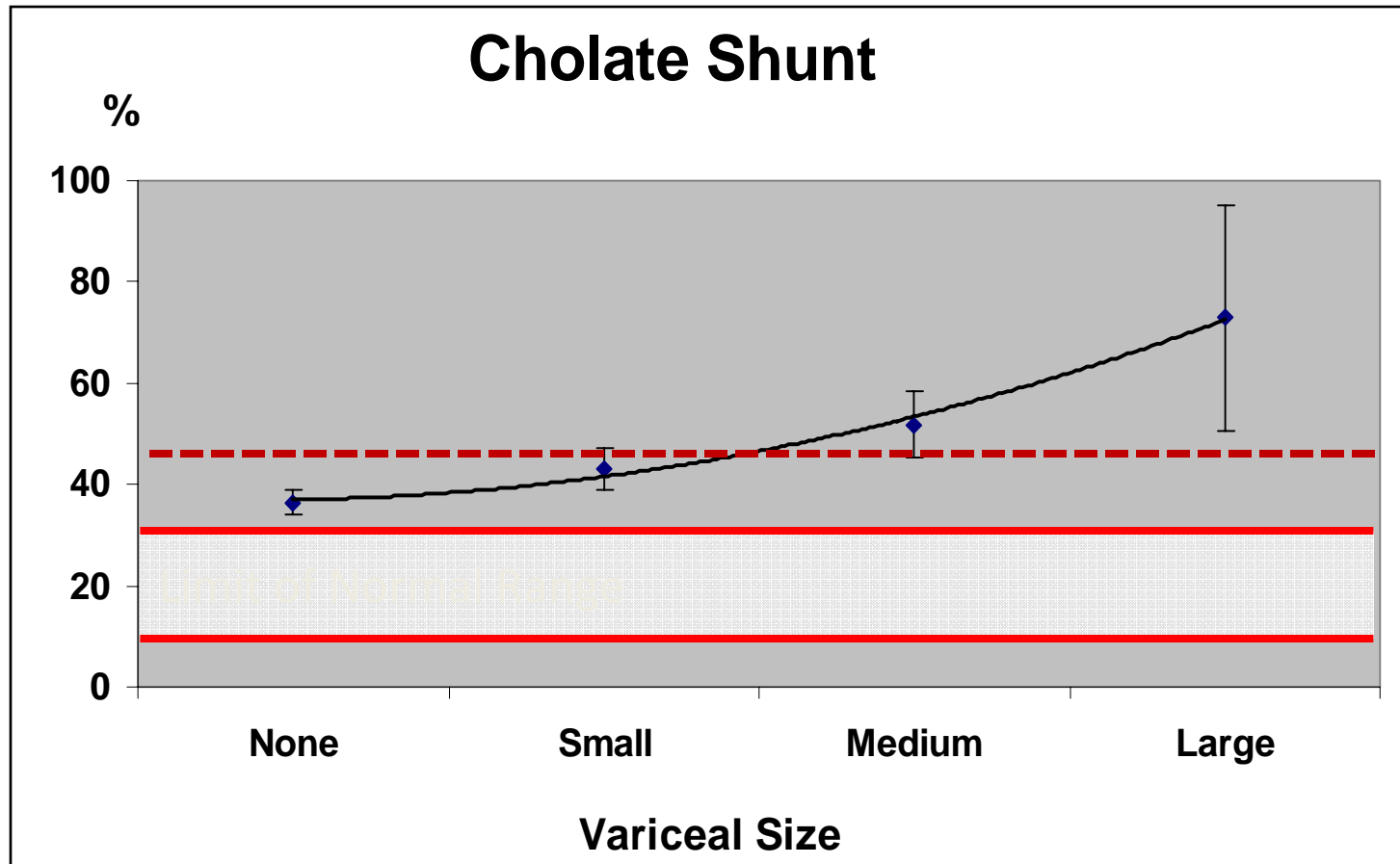
IV AUC ($\mu\text{M}\cdot\text{min}$)	PO AUC ($\mu\text{M}\cdot\text{min}$)	K Elim (min^{-1})	V Distrib (L/kg)	IV Clear (mL/min)	PO Clear (mL/min)	Shunt Fraction
149	229	0.063	0.076	285	424	67.3%

Correlation with Ishak Fibrosis Score

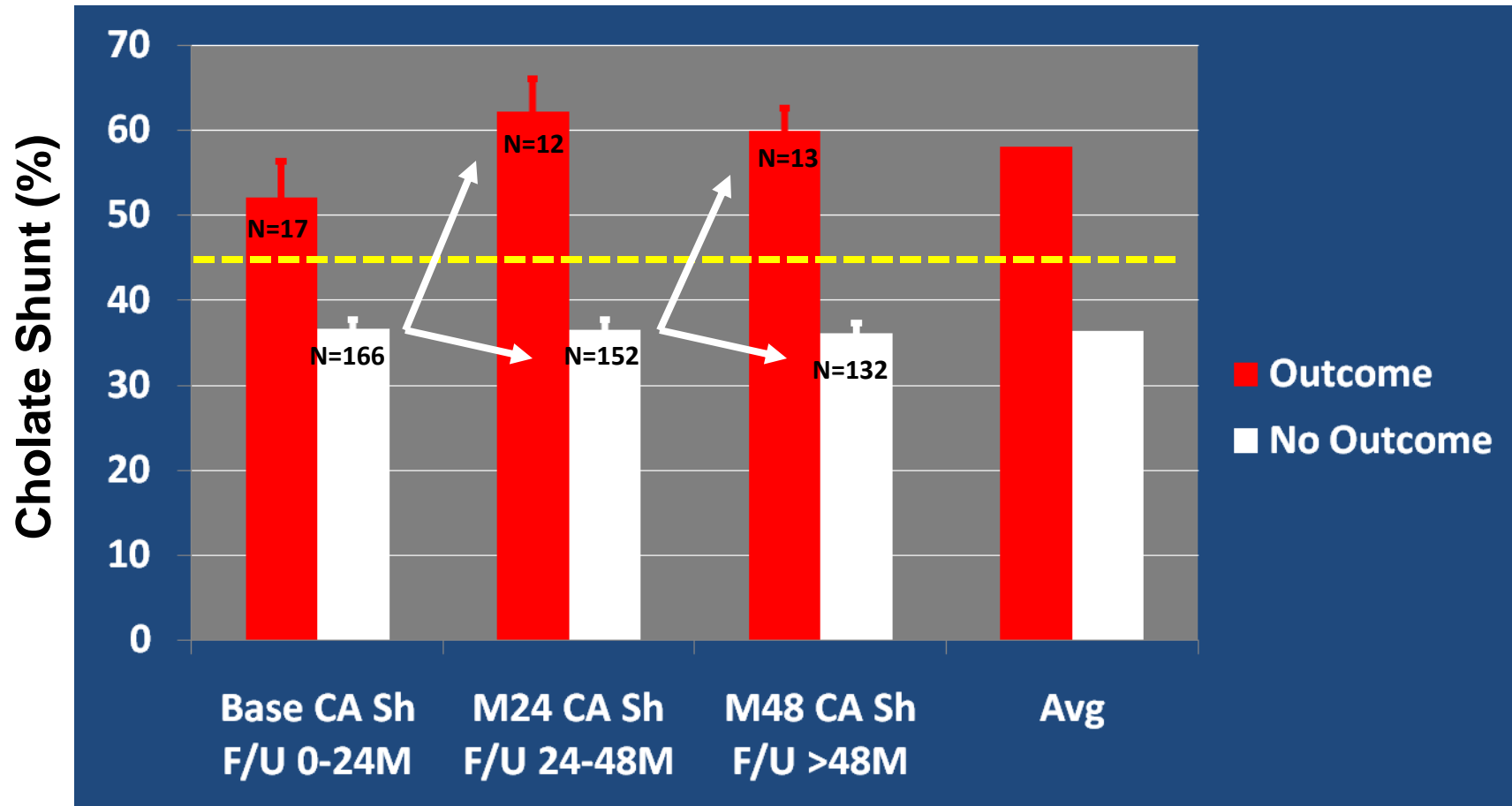


Everson GT, et al. *Alim Pharmacol Ther* 2008;27:798-809

Correlation with Variceal Size



Everson GT, et al. *Alim Pharmacol Ther* 2008;27:798-809



Cholate shunt (CA Sh) was determined at the beginning of the time interval.

No Outcome: no outcome prior to or within the f/u interval.

Outcome: first clinical outcome occurred within the f/u interval.

Cutoff = ((Avg of Mean + 2SE for Outcome)+(Avg of Mean – 2SE For No Outcome))/2.

Cutoff (yellow dotted line) for Cholate Shunt = 44.8%

Published Results with Cholate Shunt

- Utility of cholate clearances and shunt established in 548 studies of 282 patients with HCV¹.
 - Our 5-point, 90 min test is optimal¹.
 - Cholate shunt identifies patients at-risk for cirrhosis².
 - Cholate shunt identifies patients at-risk for varices².
 - Cholate shunt correlates with stage of fibrosis².
 - Cholate shunt correlates with size of varices².
 - Cholate shunt identifies a group of patients with severe hepatic dysfunction that fail to respond to antiviral therapy³.
 - Cholate shunt improves in patients with chronic hepatitis C who clear HCV with antiviral therapy³ (208 paired studies in 104 pts).
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1 Everson GT, et al. Alim Pharmacol Ther 2007;26:401-410

2 Everson GT, et al. Alim Pharmacol Ther 2008;27:798-809

3 Everson GT, et al. Alim Pharmacol Ther 2009;29:589-601

Cholate Shunt

Cutoffs with Potential Clinical Utility

Shunt 35%: Significant Fibrosis

Shunt 40%: Cirrhosis

Medium to Large Varices

Clinical decompensation over 6 years

Shunt 45%: Clinical decompensation within 2 years

**Cholate Shunt is a continuous variable
that can track individual patients over time**

Disclosure: the Cholate Shunt is currently under development as the HepQuant Dual™ test by HepQuant ,LLC founded by GT Everson, MD