Principals of Kinetic Measures of Liver Function

Focus on the Dual Cholate Clearance Test (HepQuant SHUNT)*

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Dr Everson is Equity Member and Co-Manager of HepQuant LLC.

Kinetic Measurement Definition

Kinetic Measurement: Defines a Process over time (t)

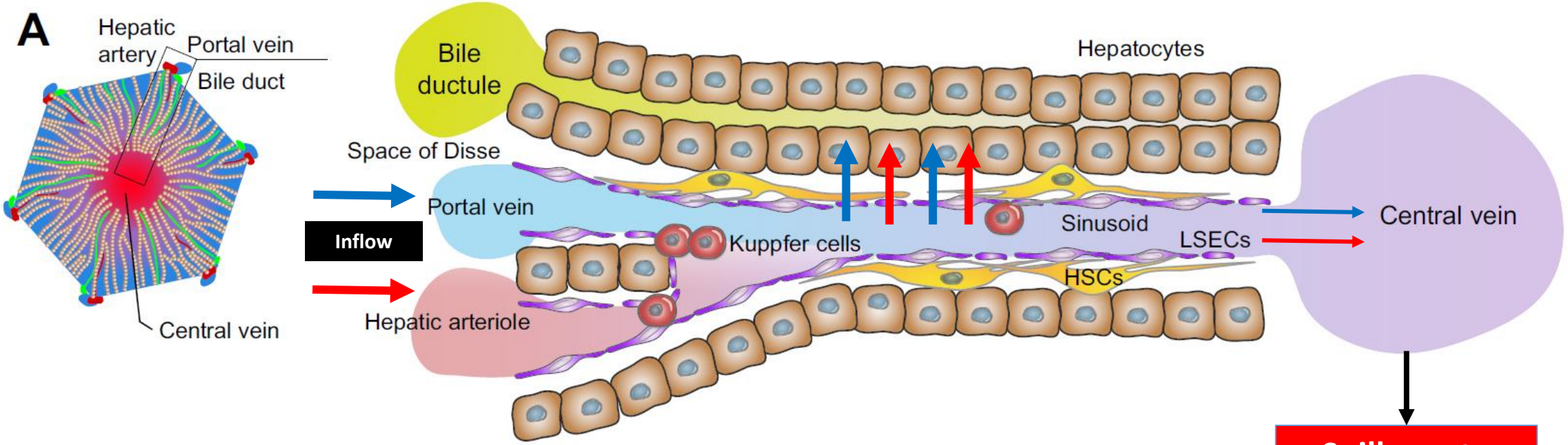
Clearance is a Kinetic Measurement: mL / t

(Volume of blood cleared of a substance over time)

The Hepatic Acinus is the Functional Unit of The Liver

Lobule

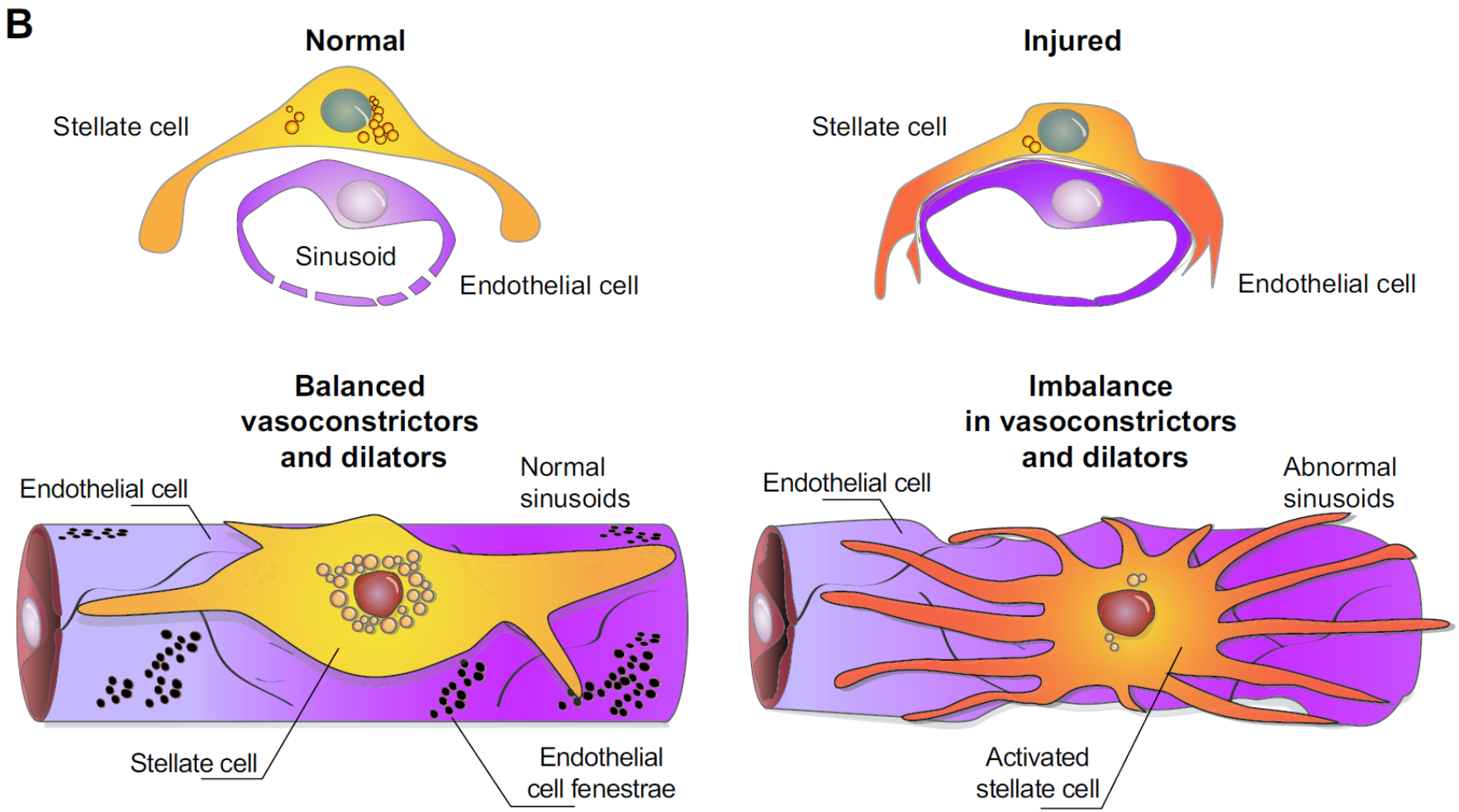
Acinus



Cholate: First-pass Extraction ≈ 0.80

Spillover to Systemic Circulation (1 – Extraction)

Iwakiri Y, Shah V, Rockey DC. J Hepatology 2014;61:912–924



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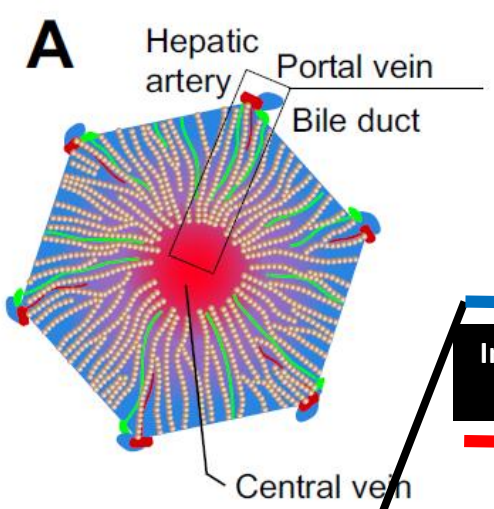
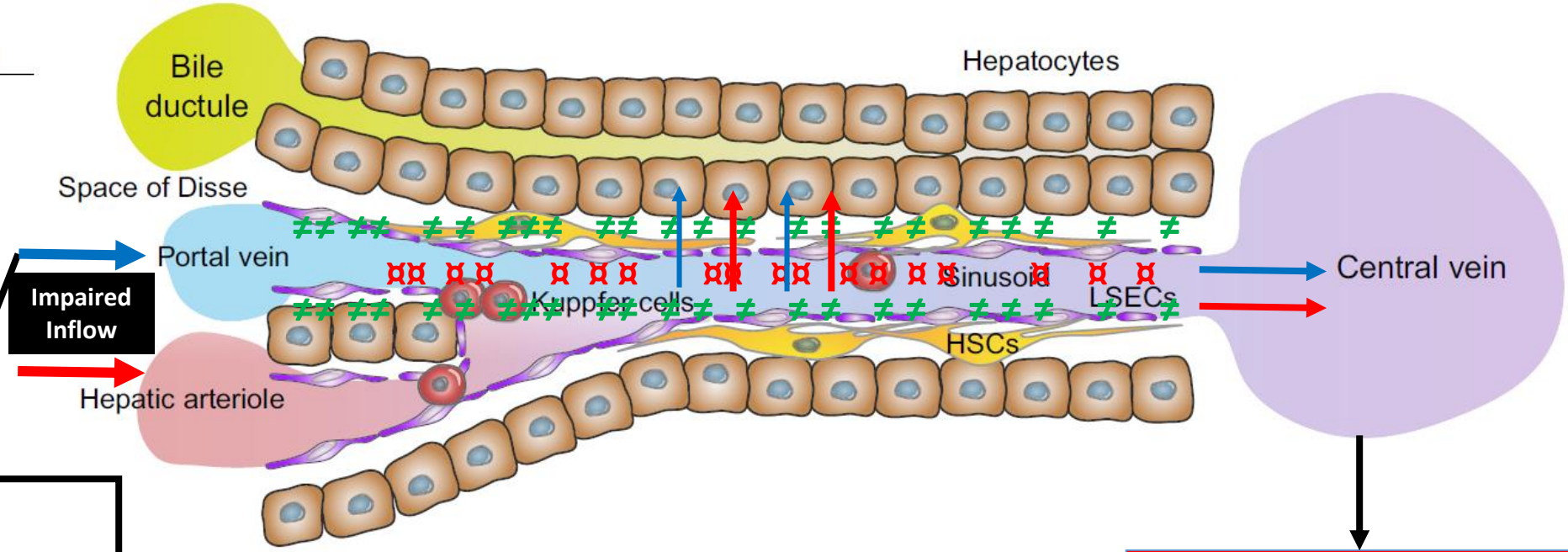
Liver Disease Targets the Acinus and Alters the Portal Circulation

Lobule

Acinus





Portal Hypertension

Portal-Systemic Collaterals Varices

↓Uptake + Collaterals Decreases Extraction

Increases Spillover (SHUNT)

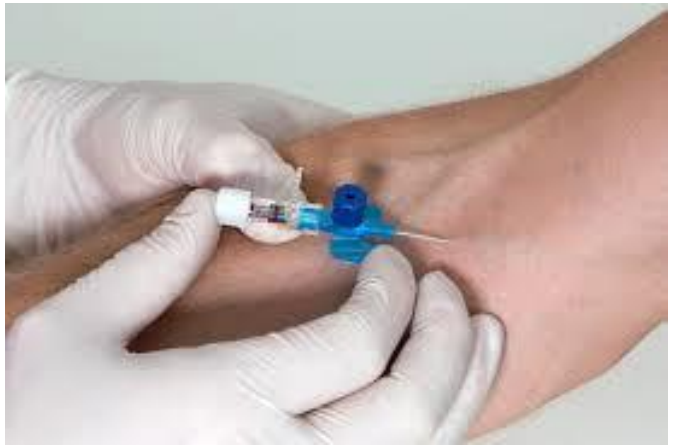
Simultaneous Measurement of Systemic and Portal Clearance of Cholate to Quantify Disease State

The HepQuant SHUNT Test

Assesses Simultaneously:

Perfusion/uptake from portal circulation
Perfusion/uptake from systemic circulation

HepQuant SHUNT Test Administration



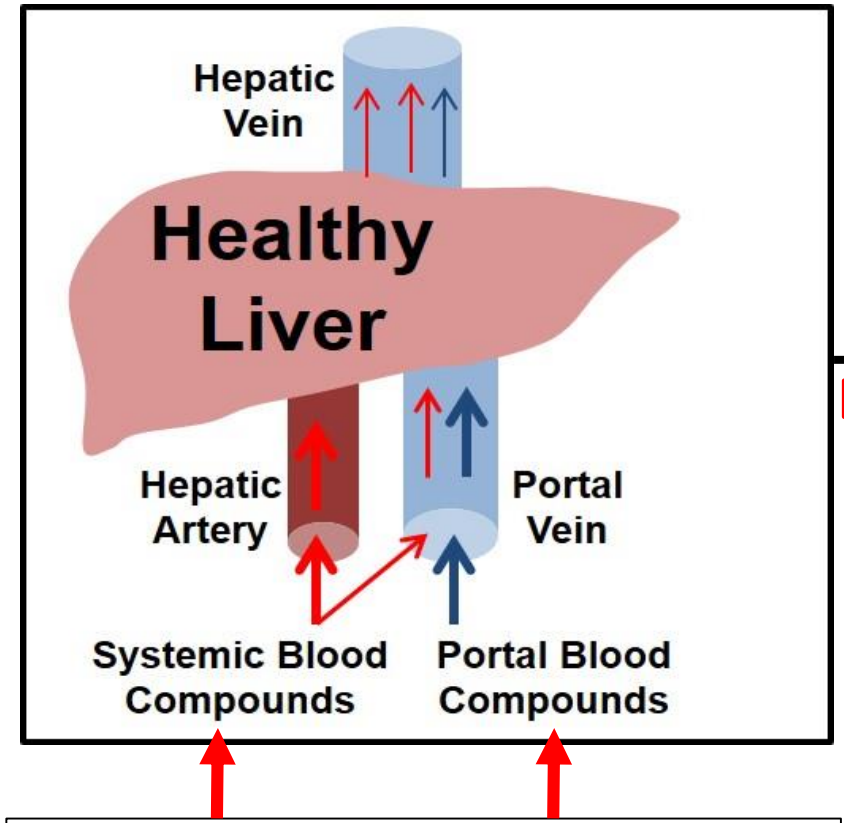
- Peripheral venous indwelling catheter
- Oral (D4-cholate, 40 mg) and IV (13C-cholate, 20 mg)
- Timed blood draws at t = 5, 20, 45, 60 and 90 minutes
- Quantifies HFRs, SHUNT, and DSI

There are two primary measurements in the HepQuant SHUNT Test

- Portal Hepatic Filtration Rate (Portal HFR)
  - Clearance 4D-Cholate (Dose AUC^{-1} kg body $weight^{-1}$)
- Systemic Hepatic Filtration Rate (Systemic HFR)
  - Clearance 13C-Cholate (Dose AUC^{-1} kg body $weight^{-1}$)

The HepQuant SHUNT Test assesses hepatocyte function (cholate uptake), systemic inflow, portal inflow, and quantifies portal-systemic spillover

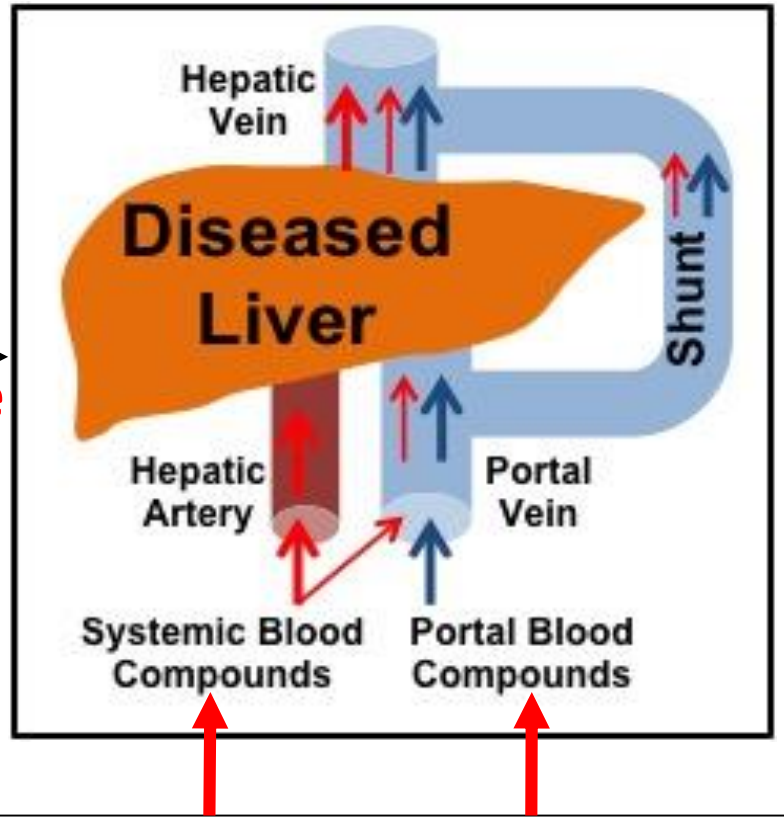
Spillover (HQ SHUNT) ~ 20%



Clearance of IV CA **Clearance of PO CA**

Liver Disease

Spillover (HQ SHUNT) 20 - 100%



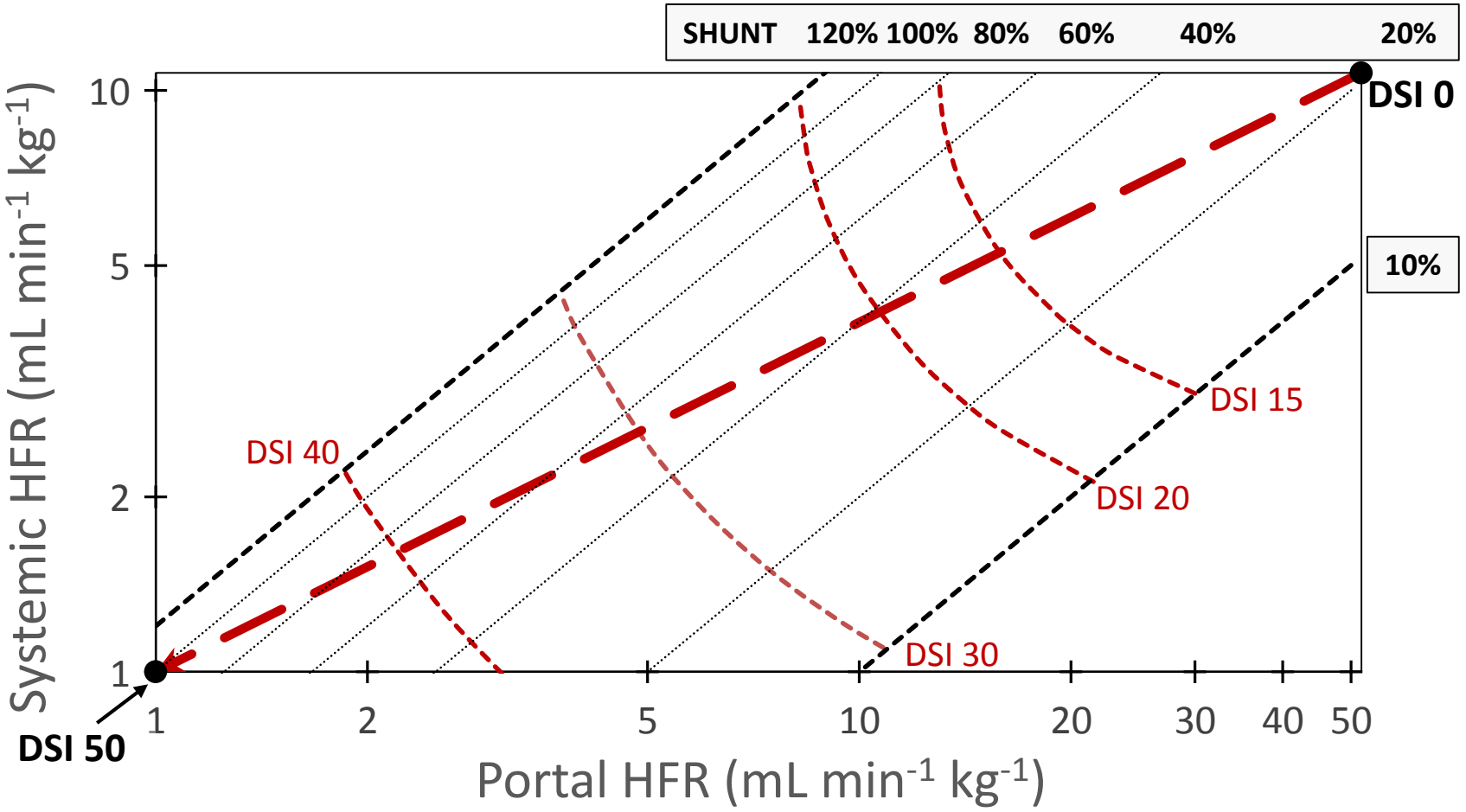
Clearance of IV CA **Clearance of PO CA**

Disease Severity Index (DSI) and SHUNT

- Disease Severity Index (DSI)
  - DSI, $\approx [f(Cl_o) + f(Cl_{iv})]$, quantifies global hepatic clearance and adjusts for the hepatic arterial buffer response
  - DSI is an Arc on the HepQuant Map

- SHUNT $\approx [(Cl_{iv}) / (Cl_o)]$
  - Quantifies relative clearances
  - Portal-systemic spillover (“SHUNT”)
  - SHUNT is a diagonal on the HepQuant Map

HepQuant SHUNT Map



Data Coordinates (X, Y): Portal HFR (horizontal (or X) axis); Systemic HFR (vertical (or Y) axis. Ln/Ln plot.
SHUNT: Diagonal dotted lines on the Map
DSI: red dashed arcs
Trajectory of disease progression from DSI 0 (upper right) to DSI 50 (lower left): heavy red-dashed arrow

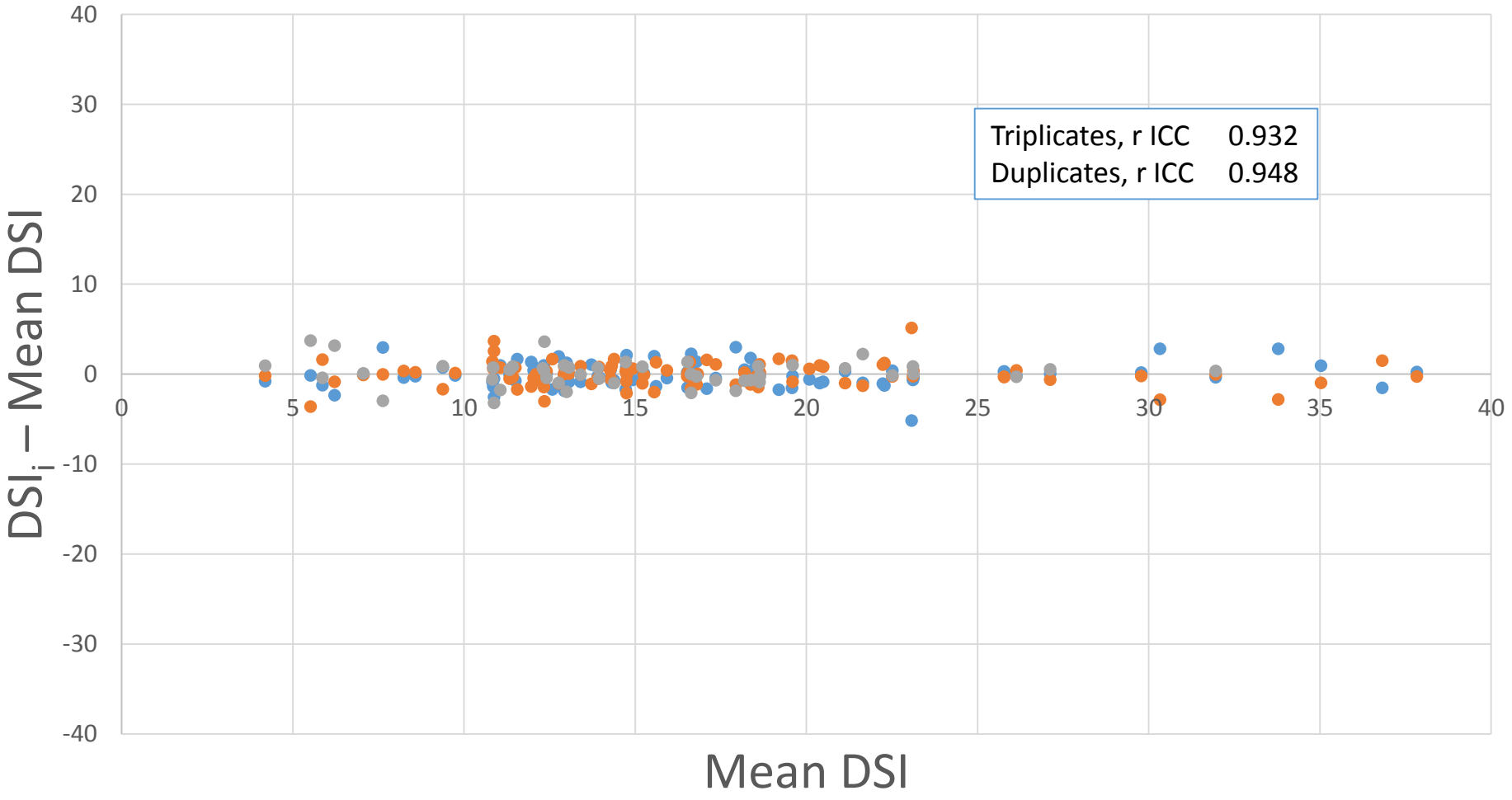
Beyond Principles: Applications

Reproducibility Studies

Study 1: Controls, HCV, NASH
HQ SHUNT three times within one month

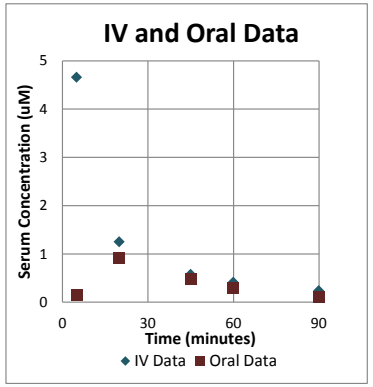
Study 2: PSC
HQ SHUNT twice within one month

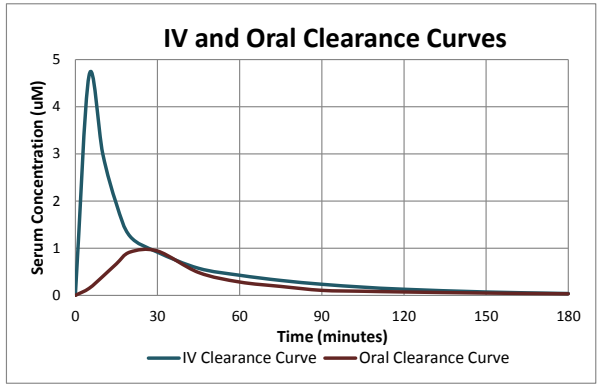
DSI Reproducibility



Markers: Orange/Blue = Visits 1 and 2; Grey = Visit 3

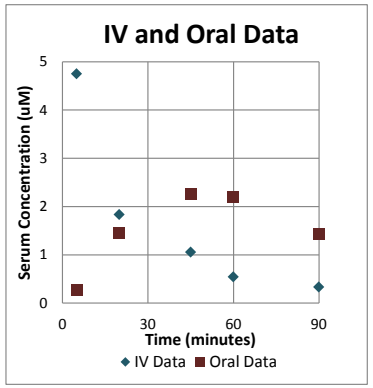
Examples of HepQuant SHUNT Test Results

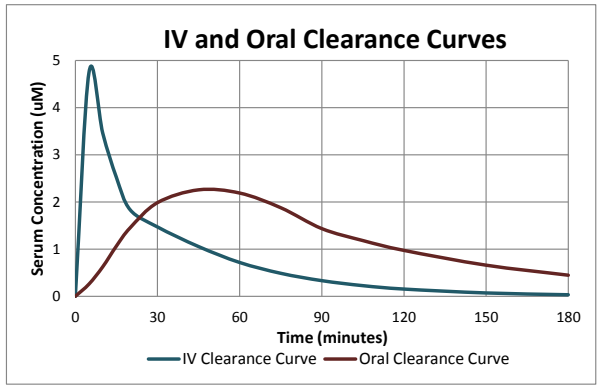




Healthy Control

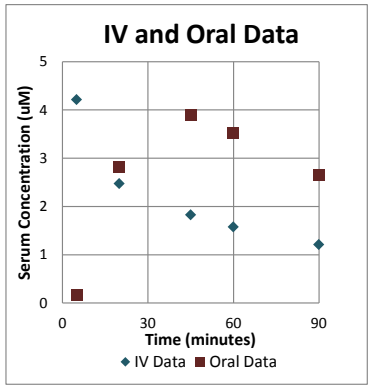
Patient Testing Results			Healthy Controls (Avg ± SD)	
K Elim:	0.088	(min-1)	0.095 ± 0.013	(min-1)
V Distribution:	0.112	(L/kg)	0.095 ± 0.036	(L/kg)
Systemic HFR:	6.93	mL/min/kg	6.6 ± 1.6	mL/min/kg
Portal HFR:	40.67	mL/min/kg	33.7 ± 7.2	mL/min/kg
SHUNT:	17.05%	(%)	21 ± 6%	(%)
STAT:	0.20	µM	0.32 ± 0.10	µM
DSI v3.3:	4.33		6.6 ± 2.8	

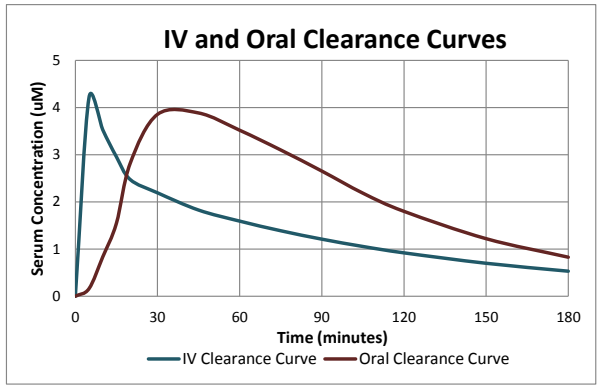




Advanced Fibrosis

Patient Testing Results		
K Elim:	0.063	(min-1)
V Distribution:	0.076	(L/kg)
Systemic HFR:	3.34	mL/min/kg
Portal HFR:	4.96	mL/min/kg
SHUNT:	67.33%	(%)
STAT:	2.50	µM
DSI v3.3:	27.28	





Decompensation

Patient Testing Results		
K Elim:	0.035	(min-1)
V Distribution:	0.108	(L/kg)
Systemic HFR:	2.04	mL/min/kg
Portal HFR:	2.48	mL/min/kg
SHUNT:	82.13%	(%)
STAT:	4.53	µM
DSI v3.3:	36.88	

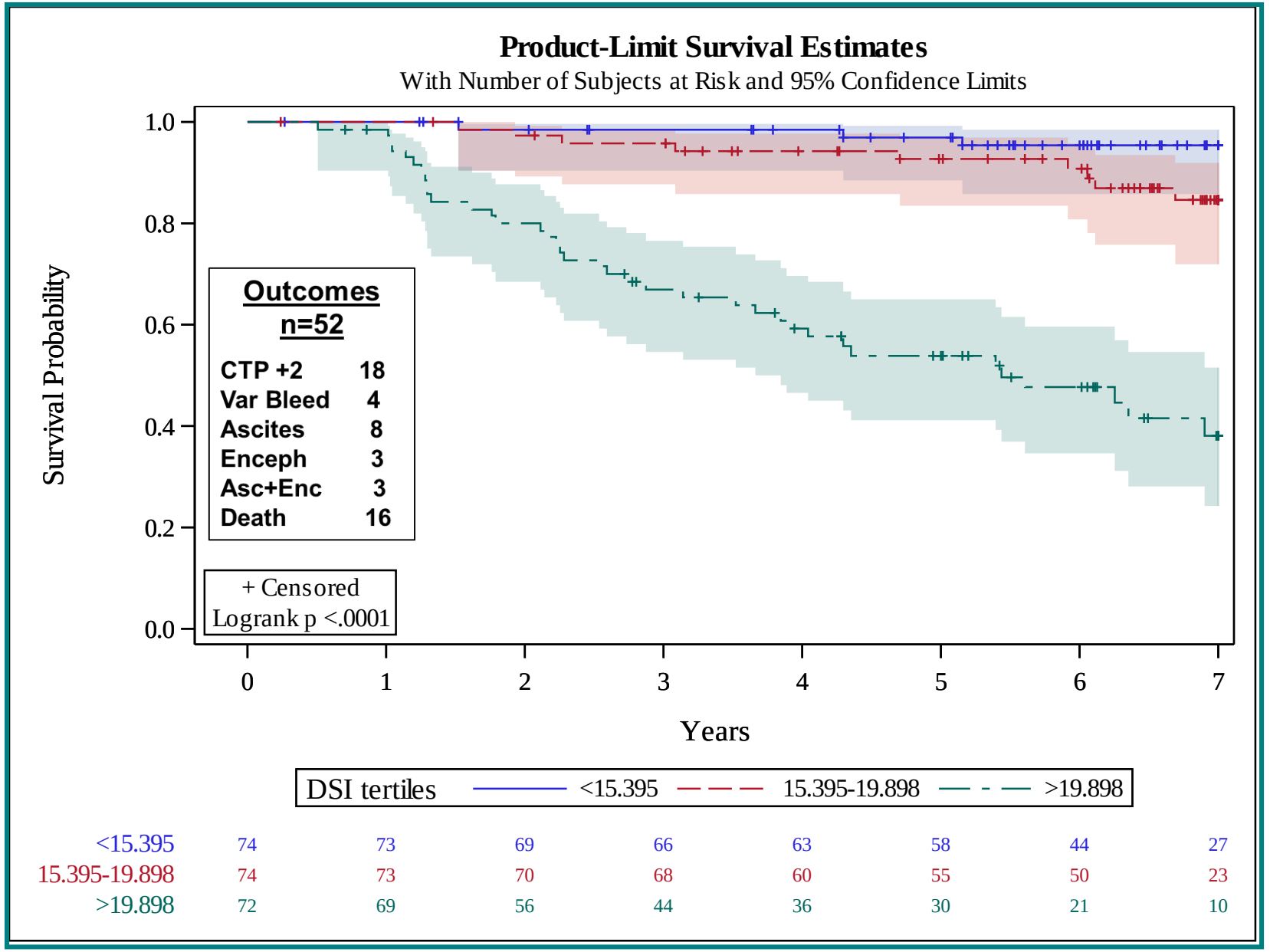
Single DSI (Mainly HCV but Similar in NAFLD/NASH)

1. > 13 Hepatic Impairment
2. > 20 Risk for cirrhosis, portal hypertension, and clinical outcome
3. > 20 Non-response to Interferon-based Rx
4. > 30 SVR after DAA Rx: "Point of No Return"
5. > 30 CTP B and C
6. > 40 Decompensation, Death, Transplantation

Change in DSI (ΔDSI)

1. HCV disease progression over 8 years
2. PSC disease progression over one year
3. Hepatic improvement after SVR
4. Hepatic impairment after Loco-Regional therapy of HCC
5. Linkage of ΔDSI to Fibrosis Progression, Progression to Cirrhosis, and Risk for future Clinical Outcomes in HCV (137 pairs over 2 years)

DSI Predicts Risk for Clinical Outcome



DSI is an Independent Predictor of Clinical Outcome

Ishak Fibrosis Stage

Variable	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value
Fibrosis ISHAK 5,6 vs 2,3,4	2.21	1.08	4.52	0.030
Platelets per unit	0.99	0.98	1.00	0.002
Age per year	0.98	0.94	1.01	0.192
Gender Male vs Female	0.87	0.46	1.64	0.669
Race Black vs Non-Hispanic, White	0.76	0.29	1.99	0.578
Race Hispanic/other vs Non-Hispanic, White	1.37	0.68	2.77	0.373

DSI

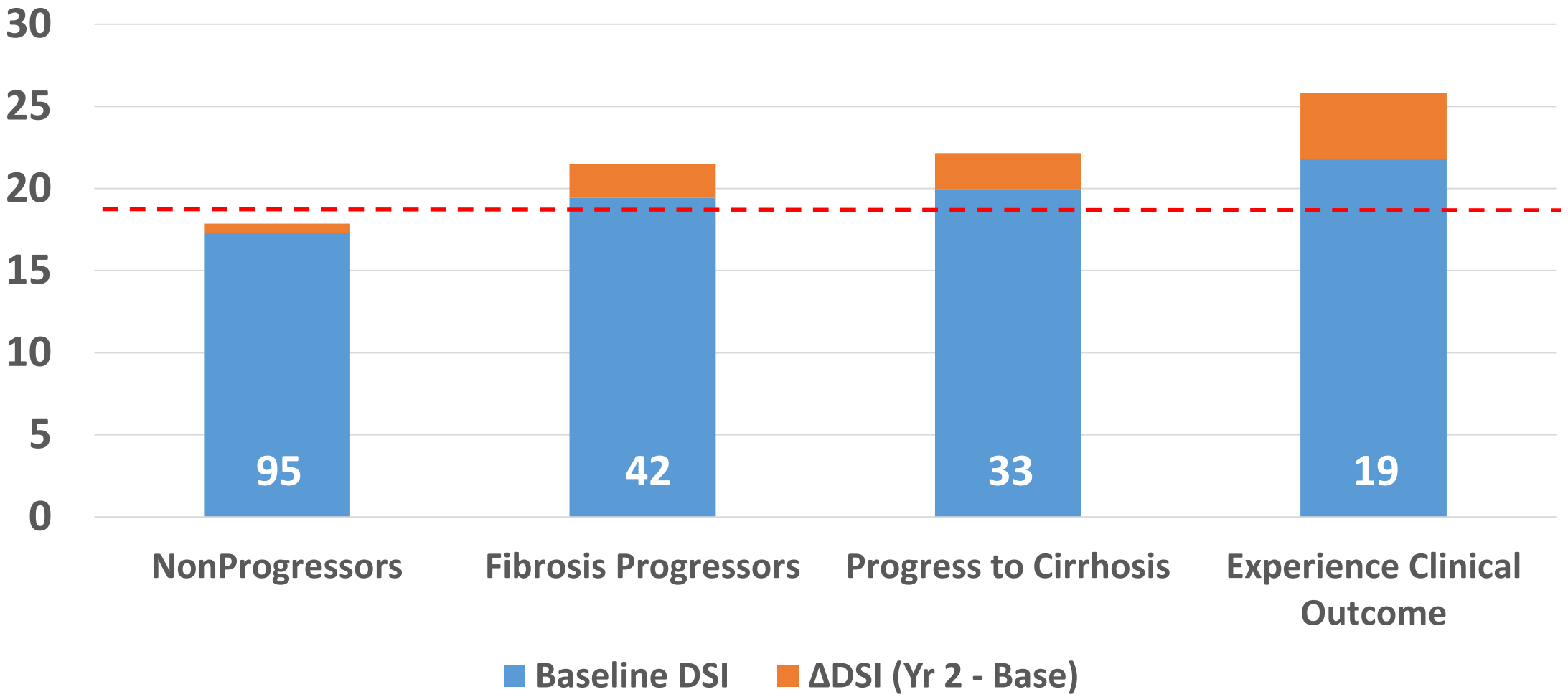
Variable	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value
DSI tertile 15.395-19.898	2.40	0.64	9.04	0.196
DSI tertile >19.898	14.01	3.84	51.08	<0.001
Fibrosis ISHAK 5,6 vs 2,3,4	1.15	0.52	2.54	0.730
Platelets per unit	0.99	0.99	1.00	0.117
Age per year	0.98	0.94	1.02	0.300
Gender Male vs Female	1.23	0.64	2.38	0.538
Race Black vs Non-Hispanic, White	0.48	0.18	1.26	0.136
Race Hispanic/other vs Non-Hispanic, White	0.97	0.47	2.00	0.940

Natural Progression

(Analogous to Placebo Arm in a Clinical Trial)

Measuring Disease Severity and Progression

(137 Patients with DSI and ISHAK Fibrosis Scores at Baseline and 2 Yr – Excluding ISHAK F6)



Treatment Effect

(Analogous to Treatment Arm in Clinical Trial)

ΔDSI after SVR

Group	N, Patients	TimeFrame	Mean ΔDSI	SD of ΔDSI
LTx F0 – F3	10	4 Weeks	-3.7*	3.9
ISHAK F2 – F6 Comp Cirrh	24	2 Years	-2.1*	2.9
LTx Cirrhosis	11	4 Weeks	-2.2*	2.6
MELD ≤10	4	36 Weeks	-4.4*	3.4
CTP B	8	60 Weeks	-4.5*	2.6
Decomp Cirrh	10	4 Weeks	0.2	2.8
HCV Cases	**67**	**Variable**	**Response Less with Most Severe Disease**	**SD of ΔDSI is similar across studies**

Use of ΔDSI to define Sample Size in Clinical Trials

Sample Sizes based on SD 4 for ΔDSI

Comparators	Mean ΔDSI Placebo group	Mean ΔDSI Treatment group	SD of ΔDSI	N per Arm 80% Power	N per Arm 90% Power
Pl vs Drug	0	1	4	128	171
Pl vs Drug	0	2	4	34	44
Pl vs Drug	0	3	4	16	21
Pl vs Drug	0	4	4	10	13

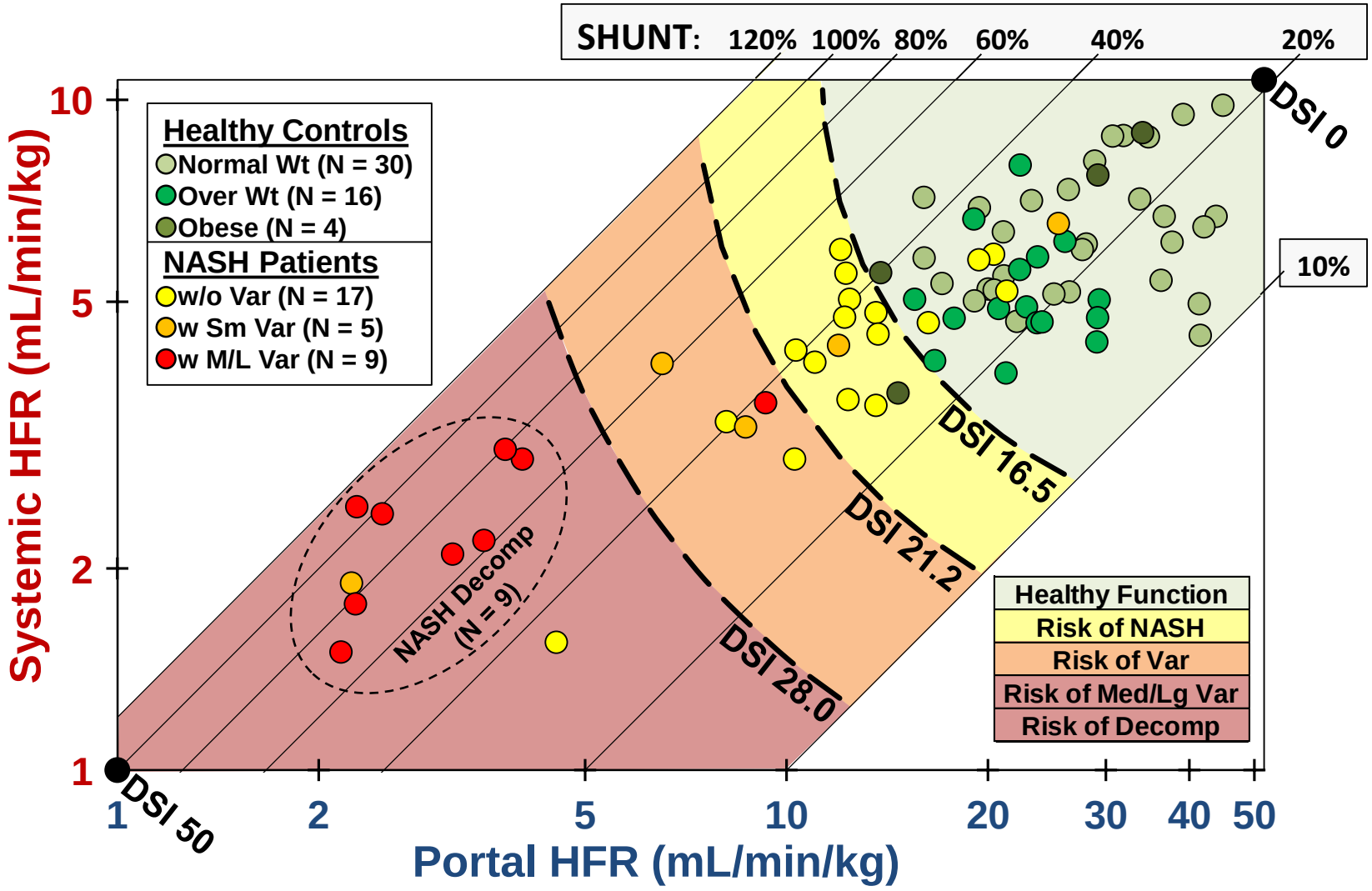
In this example, it is assumed that there would be little if any progression in the placebo arm over the time interval.

DSI can Define risk for NASH and Risk of NASH Outcomes

HQ-SHUNT (DSI) vs Liver Biopsy in NAFLD

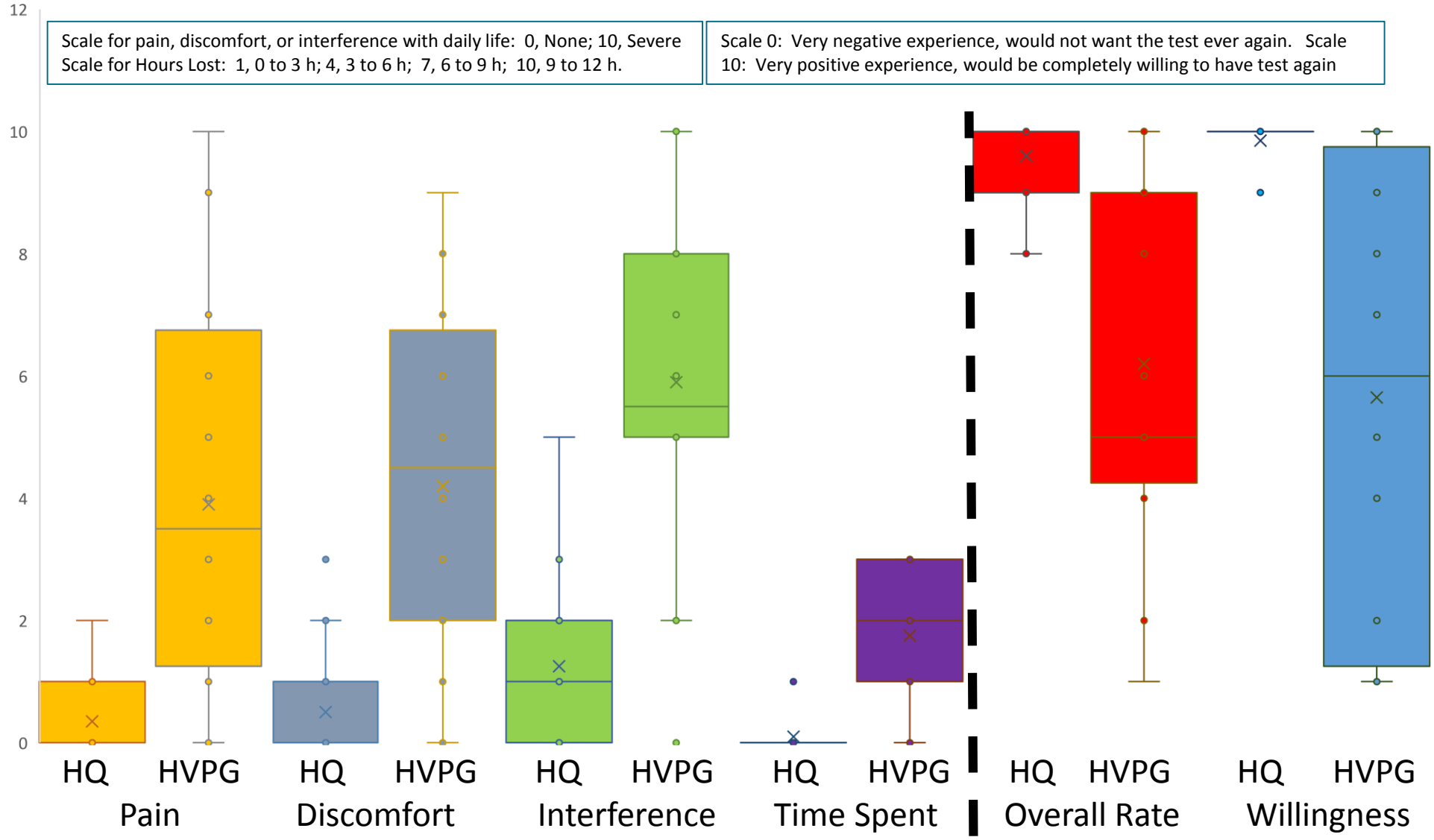
	AUROC c-statistic	optimum cutoff	Sensitivity	Specificity	PPV	NPV	Youden Index (J)
A. Ability to Diagnose NASH ina cohort of Healthy Controls (N=50) and 31 NASH Patients (N=31)							
HQ-SHUNT	0.94	DSI > 16.5	84%	98%	96%	91%	0.82
B. Ability to Identify Patients who had Medium/Large Varices (N=9) in the NASH cohort (N=31)							
HQ-SHUNT	0.92	DSI > 28	89%	91%	80%	95%	0.80
Biopsy	0.80	Cirrhosis	100%	59%	50%	100%	0.59
C. Ability to Identify Patients who had Decompensation (N=9) in the NASH cohort (N=31)							
HQ-SHUNT	0.99	DSI > 28	100%	95%	90%	100%	0.95
Biopsy	0.80	Cirrhosis	100%	59%	50%	100%	0.59

Diagnosing NASH and Patient Risk of Varices and Decompensation



Tolerability

HepQuant vs HVPG Tolerability



P < 0.0001 for all comparisons; favoring HQ over HVPG

Summary

- The Dual Cholate test (HepQuant SHUNT) characteristics
  - Plausibly linked to pathophysiology of liver disease
  - Realtime functional and physiologicial events
  - Targets Systemic and Portal InFlows Simultaneously – DSI
    - Sensitive to early changes in sinusoidal perfusion
    - Accomodates hepatic buffer responses – ie, DSI does not change
  - Quantifies Spillover from the Portal Circulation (SHUNT)
    - Over a broad range of advanced disease
  - Reproducible
  - Patient: Non-invasive, , easy to administer, high acceptance rate
- Linkage to Clinical Endpoints and Outcomes