HOW MEASURING LIVER FUNCTION CAN AID CLINICAL MANAGEMENT OF HEPATOCELLULAR CARCINOMA

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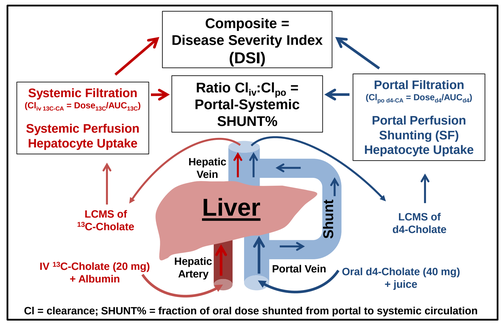
Background and Purpose

- Cost-effective screening of patients with chronic liver disease for hepatocellular carcinoma (HCC) requires identification of the high-risk subgroup[1]
- Once HCC is diagnosed, the degree of hepatic reserve dictates the anticipated tolerability of the patient to the various treatment options[1]
- Once treatment is initiated, reassessment of changes in hepatic reserve could aid in determination of doses and frequency of the prescribed therapy[1]
- HepQuant STAT and DSI are comprehensive noninvasive measures of liver function and physiology that assess hepatic reserve and risk for:
  1) Clinical outcome[2]
  2) Measure treatment effects[1]
  3) Predict drug PK[3]

HepQuant SHUNT Test Method



Cl = clearance; SHUNT% = fraction of oral dose shunted from portal to systemic circulation

HepQuant STAT =
oral d4-cholate concentration at 60 minutes adjusted for 75 kg body weight

STAT is a simple and practical measure that can easily be employed in the clinic

References

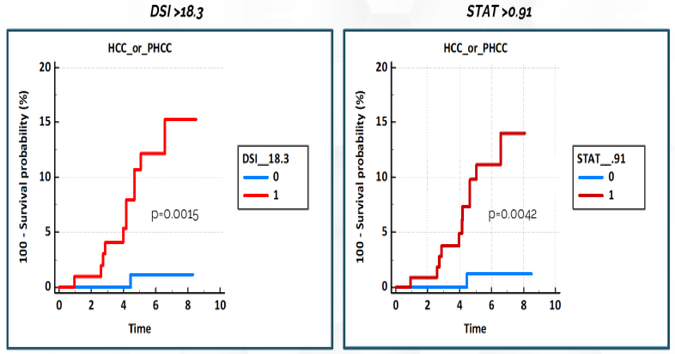
1) Hoteit, MA, Wojcieszynski, A, Currie, B, et al. Deterioration in liver function after liver-directed therapy for hepatocellular carcinoma measured by cholate clearance. *GastroHep*. 2020; 2: 232– 239. https://doi.org/10.1002/ygh2.421
2) Everson, G.T., Shiffman, M.L., Hoefs, J.C., Morgan, T.R., Sterling, R.K., Wagner, D.A., Lauriski, S., Curto, T.M., Stoddard, A., Wright, E.C. and (2012), Quantitative liver function tests improve the prediction of clinical outcomes in chronic hepatitis C: Results from the hepatitis C antiviral long-term treatment against cirrhosis trial. Hepatology, 55: 1019-1029. https://doi.org/10.1002/hep.24752
3) Kanodia, JK, et al. HepQuant SHUNT is superior to Child-Pugh in defining Hepatic Impairment for Pharmacokinetic studies: Experience with Ampreloxetine. Presented at ACCP and AASLD Annual Meetings. 2022.

Results: Study 1
HCC risk in Hepatitis C

220 subjects with HCV were free of HCC at baseline and 13 developed incident HCC at a mean of 4.66±1.42 years of follow-up.

Baseline DSI >18.3 or STAT >0.91 identified the subjects at risk for incident HCC. The relative risk for future HCC was 11.4 for subjects with baseline DSI >18.3 (12/113 vs. 1/107).

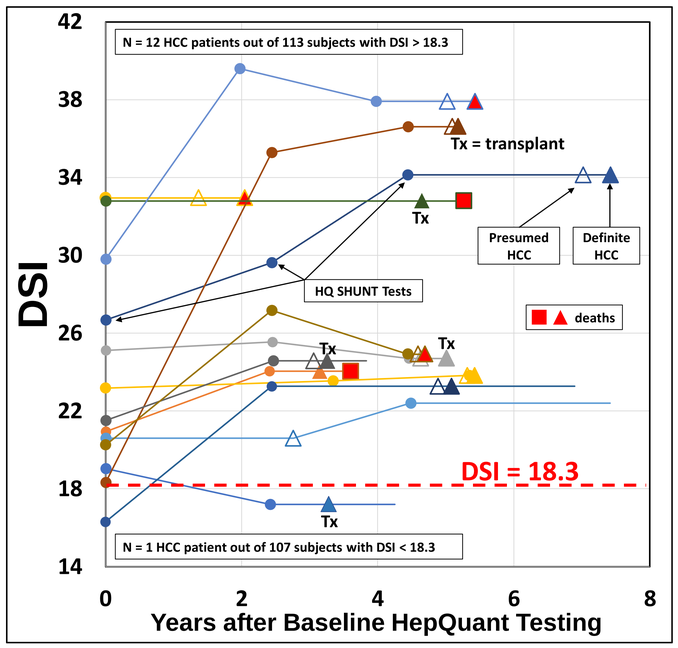
Identify Persons At-Risk for Liver Cancer – Who should be screened?



Data from the HALT-C Study – Long term follow-up of subjects with advanced fibrosis or compensated cirrhosis who were actively infected with hepatitis C.

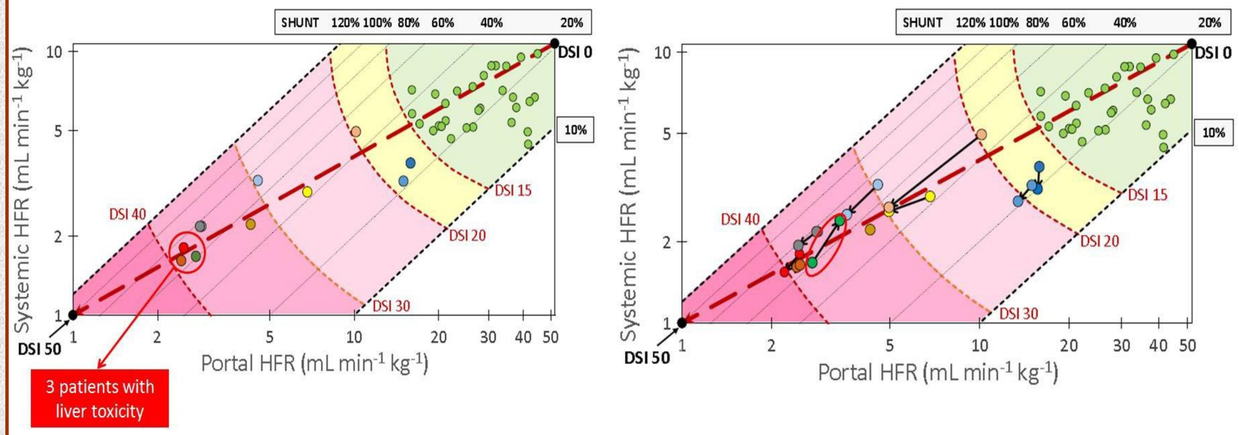
Baseline and Serial DSI Prior to HCC

Baseline DSI was 23.91 ± 5.61 and increased by 5.01 ± 5.76 prior to HCC diagnosis (p = 0.0226; two-tailored paired t-test).



Results: Study 2
Treatment Effects with Liver Directed Therapy (LDT) in HCC

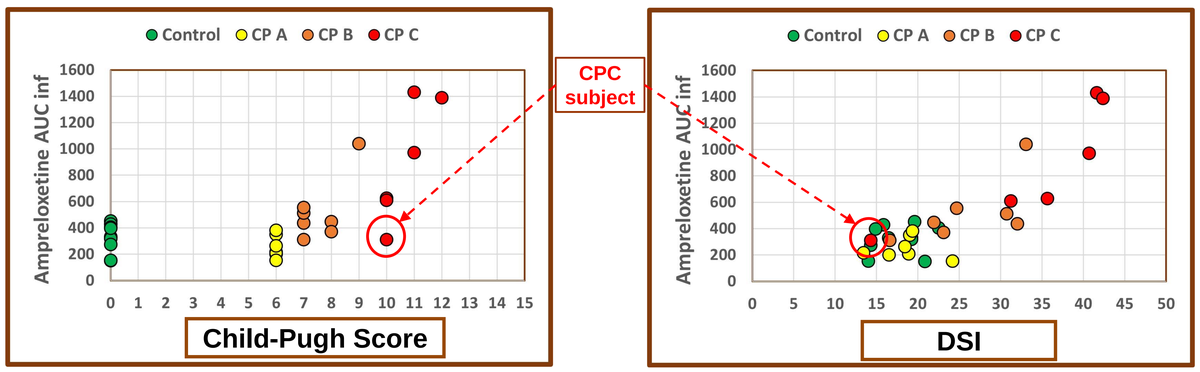
11 subjects had a complete dual cholate clearance assay at baseline at a median DSI of 32.01 (11.11-30.07). 9 were treated with TACE or SBRT and followed to assess ΔDSI at WK4-10 and hepatotoxicity.



3/5 subjects with baseline DSI>35 developed hepatotoxicity, none with DSI<35 did. All but one subject had a worsening DSI after LDT. The subject that improved had a baseline DSI>35 and still developed hepatotoxicity.

Results: Study 3
Comparison to Child-Pugh in Predicting Drug PK

30 subjects were classified by CP score, DSI and STAT assessed at baseline before treatment with Ampreloxetine. Ampreloxetine AUC correlated weakly with CP score (r^2=0.31, p=0.0013) but more strongly with SHUNT% (r^2=0.63, p<0.0001), DSI (r^2=0.65, p<0.0001), and STAT (r^2=0.65, p<0.0001).



Conclusions and Discussion

- Baseline DSI, STAT and ΔDSI may predict development of future HCC in patients otherwise stable. STAT may be useful for detecting those at risk, and DSI may be useful in monitoring post-treatment changes
- LDT may not be beneficial for patients with baseline DSI>35 or likely to progress to DSI>35 after LDT treatment. These patients may better benefit from liver transplant or less hepatotoxic interventions until transplant.
- DSI and STAT may predict drug PK better than Child-Pugh. This may be useful in understanding individual differences in response to treatment and in dose selection.