**Abstract Title: "Decreased Hepatic Reserve Determines the Risk of Varices in NASH Patients and in Chronic HCV Patients"**

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**Background/Aim:** The emerging epidemic of NASH, the most advanced form of NAFLD, requires new methods to assess patient risk for serious complications such as esophageal varices, especially the clinically relevant medium-to-large varices. Biopsies in NASH are subject to sampling error and 40% variability in staging (Ratziu, et al, 2005) and FibroScan may be inaccurate and subject to interference by steatosis (Durango, et al, 2013). HVPG is invasive and not used routinely. The minimally-invasive HepQuant®-SHUNT test provides a global measure of the Hepatic Reserve (HR). The goal of this pilot study was to determine the relationship of HR to the risk of varices in NASH patients and compare this to the risk in chronic HCV patients.

**Methods:** The HepQuant®-SHUNT test involves serum sampling prior to, and at 5, 20, 45, 60, and 90 minutes after simultaneous administration of IV cholic acid-24-$^{13}$C and oral cholic acid-2,2,4,4-d4. Clearances of labeled cholates, measured by LCMS of serum samples, were used to calculate HR. The upper limit of HR was determined from healthy controls, (N=50 with 30 normal weight (BMI 18.5-25), 16 overweight (BMI 25-30), and 4 obese (BMI>30)) and was set as 100%, while, in patients with very advanced liver disease, the apparent lower limit was set as 0%. Chronic HCV patients (N=217) enrolled in the HALT-C trial were tested and had protocol endoscopies at baseline. NASH patients (N=31 with 16 from the University of Colorado Denver and 15 from Baylor University Medical Center) were tested and endoscopy findings were captured from patient histories. Of these, 27 had biopsy-diagnosed NASH, and 4 had cryptogenic cirrhosis, concurrent obesity, and presumed late stage NASH. Chronic HCV patients had a range of METAVIR fibrosis stages, F1 (N=19), F2 (N=61), F3 (N=44), and F4 (cirrhosis, N=93, all compensated) and NASH patients had a range of Brunt-Kleiner fibrosis stages, F1 (N=4), F2 (N=4), F3 (N=5), and F4 (cirrhosis, N=18, of which 9 were decompensated).The ability of HR to assess the risk for any size varices and for medium-to-large varices was evaluated by logistic regression analysis and by ROC analysis (c-statistic and the sensitivity, specificity, PPV, NPV at the optimum cutoff defined by the maximum Youden Index).

**Results:** In the HCV cohort, the prevalence of any size varices was 34% and of medium-to-large varices was 10%, while in the NASH cohort the prevalence of any size varices was 45% and of medium-to-large varices was 29%. Univariate logistic regression models showed that HR was a highly significant predictor of any size varices ($p<0.0001$) and medium-to-large varices ($p<0.0001$) in HCV patients, and of any size varices ($p=0.0037$) and medium-to-large varices ($p=0.002$) in NASH patients. In these logistic regression models, the probability that a patient would have any size varices would exceed 50% in HCV patients when their HR declined to <50.6%, and in NASH patients when their HR declined to an almost identical value of <50.7%. The probability of medium-to-large varices would exceed 50% when there was a further decline in HR to <33.6% in HCV patients, and a similar decline to <39.1% in NASH patients.

By ROC analysis, the decline in HR could identify NASH patients at higher risk of any size varices (c-statistic 0.87) and the optimum cutoff was an HR<59.6% (sensitivity 86%, specificity 82%, PPV 80%, NPV 88%, Youden Index 0.68). Further decline in HR could identify NASH patients at higher risk of medium-to-large varices (c-statistic 0.93) and the optimum cutoff was an HR<50.3% (sensitivity 89%, specificity 91%, PPV 80%, NPV 95%, Youden Index 0.80). Similarly, the decline in HR could identify HCV patients at higher risk of any size varices (c-statistic 0.71) and the optimum cutoff was an HR<57.9% (sensitivity 61%, specificity 81%, PPV 63%, NPV 80%, Youden Index 0.42). HR could identify HCV patients at risk of medium-to-large varices (c-statistic 0.82) and the optimum cutoff was an HR<56.8% (sensitivity 77%, specificity 76%, PPV 27%, NPV 97%, Youden Index 0.53). Again, the cutoffs for predicting higher risk of varices were similar in NASH and HCV patients.

**Conclusion:**

This pilot data suggests that the decline in Hepatic Reserve could be utilized to assess the risk for any size varices and the risk for medium-to-large varices in NASH patients.

The risk for varices was related to the decline in Hepatic Reserve in a very similar manner in NASH patients and in chronic HCV patients, suggesting that the same pathophysiological mechanisms underlie both types of liver disease.