The Disease Severity Index from HepQuant DuO and Likelihood for Large Esophageal Varices in the SHUNT-V Study

M.P. McRae[1], S.M. Helmke[2], and G.T. Everson[2] for the SHUNT-V Investigators

[1]Custom Diagnostic Solutions LLC, Houston, TX, USA; [2]HepQuant LLC, Denver, CO, USA

Background

- Endoscopy (EGD) is indicated in patients with cirrhosis to check for large esophageal varices (LEVs) that need treatment.
- Prevalence of LEVs at EGD in Child-Pugh (CP) A cirrhosis is ~10%.
- The HepQuant SHUNT test quantifies liver function and portal-systemic shunting.
- An oral-only version (HepQuant DuO) was developed to simplify test administration and reduce variability.

Aims

- To evaluate the diagnostic performance of HepQuant DuO Test in ruling out LEVs in CP A cirrhosis
- To compare performance of HepQuant DuO and HepQuant SHUNT tests

Methods

Subjects

- 238 patients with CP A cirrhosis in the SHUNT-V Study
  - 50% MASLD/MASH, 24% HCV, 18% alcoholic liver disease
  - 64% obese, 85% overweight, 54% diabetes

SHUNT Test Administration

- 13C-cholate injected by IV and d4-cholate administered orally
- Blood sampled at 0, 5, 20, 45, 60, 90 min. for serum cholate

HepQuant Test Versions

- SHUNT V1.1: 13C- and d4-CA concentrations at 20, 45, 60, and 90 min. were calculated based on cubic spline and exponential fits [1]
- DuO: only d4-CA concentrations at 20 and 60 min., calculated based on compartmental model [2]

Test Parameters

- Disease severity index (DSI), portal-systemic shunt (SHUNT%), Hepatic Reserve, and Portal Hepatic Filtration Rate (HFR_P)
- DSI cutoff of ≤18.3 was prespecified based on >95% sensitivity for LEVs in the HALT-C Trial QLFT ancillary study

Statistical Analysis

- Differences between subgroups analyzed by ANOVA (continuous data) and Chi-square (categorical data)
- DSI from lean and overweight controls plotted alongside subjects with no, small, or large esophageal varices
- Diagnostic performance for ruling out LEVs (AUROC, sensitivity, specificity, PPV, NPV)
- AUROCs for DuO and SHUNT V1.1 for ruling out LEVs compared by DeLong method
- Univariate logistic regression of DSI for presence of LEVs

Results

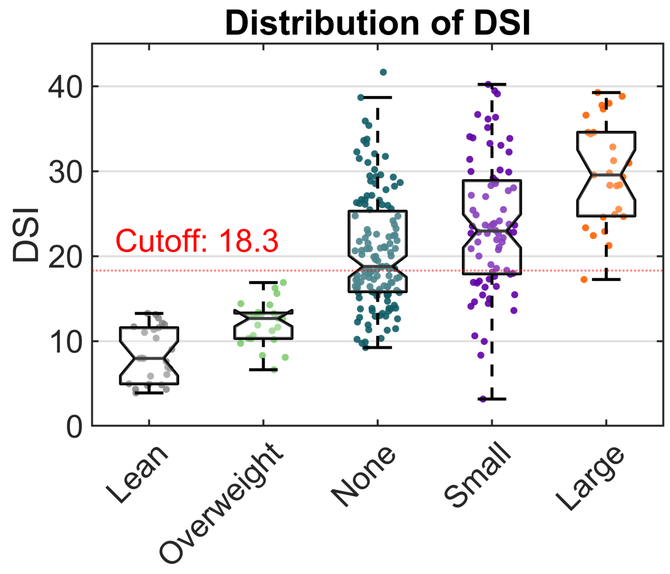
HepQuant DuO parameters were sensitive in detecting presence and size of varices.

	All Subjects (N=238)	No Varices (N=135)	Small Varices (N=76)	Large Varices (N=27)	p-value
Laboratory Values					
Albumin, g dL^{-1}	4.23 ± 0.43	4.31 ± 0.41	4.18 ± 0.45	4.00 ± 0.42	**0.0014**
Alk. Phos., U L^{-1}	100.53 ± 51.86	94.61 ± 37.64	102.87 ± 69.34	123.11 ± 50.22	**0.0294**
ALT, U L^{-1}	38.42 ± 34.24	39.90 ± 41.00	37.32 ± 24.28	34.22 ± 18.15	0.6945
AST, U L^{-1}	42.11 ± 24.98	41.03 ± 25.69	42.47 ± 25.28	46.44 ± 20.56	0.5855
Bilirubin, mg dL^{-1}	0.75 ± 0.44	0.70 ± 0.41	0.74 ± 0.43	1.00 ± 0.52	**0.0042**
Creatinine, mg dL^{-1}	0.90 ± 0.29	0.89 ± 0.25	0.93 ± 0.38	0.89 ± 0.19	0.6377
Platelets, $\times 10^3$ μL^{-1}	152 ± 68	169 ± 68	142 ± 61	97 ± 53	**<0.0001**
Prothrombin time, INR	1.09 ± 0.15	1.08 ± 0.13	1.11 ± 0.18	1.13 ± 0.10	0.1076
APRI	0.87 ± 0.66	0.72 ± 0.53	0.87 ± 0.62	1.56 ± 0.92	**<0.0001**
FIB-4	3.63 ± 2.67	2.98 ± 2.06	3.70 ± 2.23	6.61 ± 4.10	**<0.0001**
Clinical Scores					
Child-Pugh score	5.14 ± 0.35	5.11 ± 0.32	5.12 ± 0.33	5.33 ± 0.48	**0.0076**
MELD score	7.84 ± 2.22	7.58 ± 1.93	8.15 ± 2.69	8.27 ± 1.93	0.1198
HepQuant DuO					
DSI	22.56 ± 7.53	20.49 ± 6.64	23.64 ± 7.71	29.88 ± 6.07	**<0.0001**
SHUNT% (%)	38.57 ± 15.61	34.23 ± 13.29	40.97 ± 16.30	53.52 ± 14.02	**<0.0001**
Hepatic Reserve (%)	71.33 ± 19.23	76.84 ± 17.05	68.27 ± 19.18	52.40 ± 15.94	**<0.0001**
HFR_P (mL/min/kg)	11.02 ± 6.86	12.54 ± 6.29	10.29 ± 7.70	5.52 ± 2.94	**<0.0001**

Applying the DSI ≤18.3 cutoff to SHUNT-V subjects would have missed 1 case and prevented 84 EGDs.

Diagnostic Performance (95% CI) of DuO (DSI ≤18.3) in SHUNT-V CP A Subjects (N=238)	
Sensitivity	0.96 (0.81-1.00)
Specificity	0.39 (0.33-0.46)
Positive Predictive Value	0.17 (0.15-0.19)
Negative Predictive Value	0.99 (0.92-1.00)
Positive Likelihood Ratio	1.59 (1.39-1.81)
Negative Likelihood Ratio	0.09 (0.01-0.65)
Missed LEVs, n (%)*	1 (3.7%)
EGDs Prevented, n (%)	84 (35.3%)

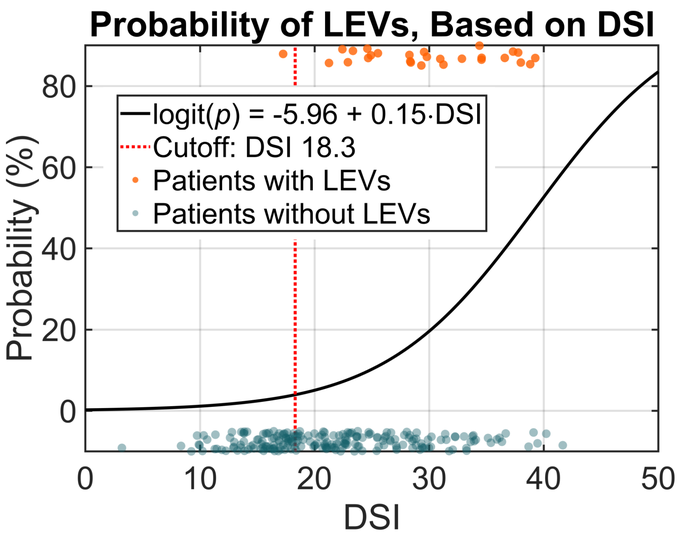
Monotonic, stepwise increase in DSI with increasing risk for LEVs



DuO was equivalent to SHUNT V1.1 in detecting the presence of LEVs.

Pairwise comparison of AUROC for DSI in detecting LEVs in SHUNT-V CP A (N=238)		
	AUROC (95% CI)	p value
DuO	0.809 (0.737-0.882)	0.3169
SHUNT V1.1	0.817 (0.749-0.885)	-

DSI from DuO demonstrated significant association with finding LEVs at endoscopy (p<0.001).



Conclusions

- **HepQuant DuO test parameters of liver function and physiology correlate with presence and size of esophageal varices.**
- **Knowing the likelihood that a given DSI is associated with a particular risk of LEVs is highly relevant to clinical decision making.**
- **DuO and SHUNT V1.1 were statistically equivalent in the detection of LEVs.**
  - **DuO missed one LEV case that was detected by SHUNT V1.1.**
  - **Application of DSI ≤18.3 would have avoided EGDs in 35% for DuO versus 31% for SHUNT V1.1.**
- **DuO is easier to administer and less invasive, thus, having the potential to be more widely accepted by care providers administering the test and by patients receiving the test.**

HEPQuant Transforming Liver Health

References

[1] Everson GT et al. Aliment. Pharmacol. Ther. 2007; 26:401-410.
[2] McRae MP et al. Transl. Res. 2023; 252:53-63.

Contact Information

Shailesh Chavan (CMO): shailesh.chavan@hepquant.com
Steve M. Helmke (CSO): steve.helmke@hepquant.com
Michael P. McRae: michael.mcrae@hepquant.com

Disclosures

MPM is a paid consultant for HepQuant LLC. SMH and GTE are employees and equity members of HepQuant LLC. All authors have provisional patents pending. HepQuant tests are not FDA approved and are for investigational use only under FDA guidelines for investigational device exemption (IDE).