Protocol title: Non-invasive Evaluation of Portal Hypertension in Patients With Compensated Advanced Chronic Liver Disease by Liver Stiffness Measurement Using Liver Incytes

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Non-invasive Evaluation of Portal Hypertension in Patients with Compensated Advanced Chronic Liver Disease by Liver Stiffness Measurement Using Velacur

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Study Design: Prospective Observational Study

Number of Patients: 200 patients with compensated cirrhosis

1. Introduction:

For long, cirrhosis has been considered as end-stage liver disease but it is increasingly being realized that the 1-year mortality in cirrhosis varies widely, from 1% to 57%, depending on the occurrence of clinical decompensating events.[1] Histopathologists have proposed that the histological term cirrhosis should be substituted by advanced liver disease, to underline the dynamic processes and variable prognosis of the disorder.[2] A new term, compensated advanced chronic liver disease (cACLD) defining patients in the early phases of severe chronic liver disease, including both patients with severe fibrosis or pre-cirrhotic patients and patients with compensated cirrhosis is considered very helpful for both clinical practice and research purposes. Cirrhosis should no longer be regarded as a terminal disease and the concept of a dynamic process is increasingly accepted. A prognostic clinical subclassification with four distinct stages has been proposed with substantially differing likelihoods of mortality (Figure 1).

Currently, the management of patients with cACLD includes assessment for severity of portal hypertension and risk stratification. Cirrhosis is currently classified into two main prognostic stages: compensated and decompensated cirrhosis.[1, 3] This classification depends on the presence or absence of clinically evident decompensating events (specifically ascites, variceal hemorrhage, and encephalopathy), with a median survival in the compensated stage that exceeds 12 years, while it is only 1.8 years in patients who develop decompensation (Figure).[3]

Figure. Stages of compensated advanced chronic liver disease and liver-related clinical events

	Advanced Liver Disease				
	Compensated Advanced Chronic Liver Disease			Decompensated Cirrhosis	
	Advanced Fibrosis	Compensated Cirrhosis			
Stage	F3-F4	Stage 1	Stage 2	Stage 3	Stage 4
Clinical Manifestations	No varices No ascites	No varices No ascites	Varices No ascites	Ascites ± Varices	Bleeding ± Ascites
Liver-related mortality	Less likely	1%	3%	20%	57%
Risk of HCC	Very Low	3% per year			
Time-interval	1/3rd progress over 3-4 yrs	? Rate of progression →			

The Child-Turcotte-Pugh (CTP) classification has been used to stratify patients with cirrhosis.[4] Patients with cirrhosis belonging to the CTP-A class are compensated, whereas those in the CTP-B/C class are mostly decompensated.[4] Similarly, Model for End-Stage Liver Disease (MELD) is a reliable measure of mortality risk in patients with end-stage liver disease and used to help prioritize organ allocation for transplant.[5, 6] However, MELD scores of <10, typically seen in CTP-A, are unlikely to have prognostic value as the likelihood of clinical events in a 1 to 2-year

time frame is low.[1, 7, 8] Therefore, both CTP and MELD scores best stratify cirrhosis patients with decompensation and have limited use in compensated cirrhotics who have no liver-related symptoms.

Patients with compensated cirrhosis are substaged based on the severity of portal hypertension (Figure 1).[9] However, measurement of portal pressure through direct puncture of the portal vein is risky and not routinely performed. Therefore, portal pressure is assessed indirectly by calculation of hepatic vein pressure gradient (HVPG) by measuring the difference between wedge and free hepatic venous pressure.[10-12] The normal value of HVPG is between 3 and 5 mmHg.[11, 12] Currently, the severity of portal hypertension is defined as mild when HVPG is ≥6 but <10 mm Hg, ≥10 mm Hg as clinically significant portal hypertension (CSPH), and ≥12 mm Hg as severe portal hypertension (SPH) .[13] Evaluation of a compensated cirrhotic by HVPG is ideal for risk stratification as CSPH is associated with an increased risk of varices, decompensation (ascites, variceal hemorrhage and/or hepatic encephalopathy) and hepatocellular cancer.[14-16] However, measurement of HVPG is cumbersome, invasive, non-standardized and often limited to tertiary care centers due to limited expertise.[17] Therefore, there is a need for non-invasive tools that can estimate HVPG easily, reproducibly and with high diagnostic accuracy. It is thus not a surprise that some investigators have examined the prognostic value of AST-to-Platelets Ratio Index (APRI) and fibrosis-4 (FIB-4) for prediction of adverse clinical outcomes related to portal hypertension.[18, 19]

Liver stiffness measurement (LSM) by vibration controlled transient elastography (VCTE) is currently used for non-invasive diagnosis liver fibrosis in patients with chronic liver disease. In patients with cirrhosis, LSM is likely indicative of cumulative stiffness from underlying liver fibrosis and portal hypertension. In addition, some studies have reported a good correlation between LSM and HVPG and its ability to detect CSPH.[20, 21] In fact, in the recent Baveno conference (Baveno VI), a screening endoscopy was not recommended in patients with LSM <20 kilopascals (kPa) and platelet count >150,000/μl due to very low risk of having varices at high risk of bleeding.[21, 22] In one study that examined the prognostic accuracy of HVPG and serum fibrosis biomarkers, both measures worked equally well in predicting clinical outcomes.[19]

FibroScan® is a commonly used diagnostic device based on VCTE.[23, 24] While the use of FibroScan® in liver clinics is attractive as a point of care exam that can provide immediate indirect data about hepatic steatosis and fibrosis in the clinic, advancement in quantitative ultrasound technology may now allow even more detailed and directed non-invasive assessment of these measures of liver disease.

Velacur offers the ability to simultaneously and non-invasively measure Attenuation Coefficient Estimate (ACE) as a quantitative measure of ultrasound attenuation[25] and detection of hepatic steatosis in addition to LSM which measures deep volumetric liver elasticity using steady state shear waves, known as shear wave absolute viboelastography (SWAVE). This technology enables measurements of liver elasticity to a depth equal to the B-mode image, or in excess of 15 cm. The system consists of an ultrasound machine, a vibration device to excite shear waves in the patient and an ultrasound transducer. The vibration device induces shear waves in the liver at four different frequencies between 40Hz and 70Hz simultaneously. The ultrasound volume is acquired through the ribs at the same location as a typical transient elastography (TE) measurement. Volumes are collected in a fan of approximately 15 degrees and taken at a depth up to 15cm, which much deeper than Fibroscan® measurement (6 cm), and allows for much larger sample measurement (100,000 mm^3) versus that measured by Fibroscan® (3,140 mm^3).

The natural history of chronic liver disease with advanced fibrosis/ cirrhosis across the different clinical stages of cirrhosis (Figure) is currently not well understood. Therefore, non-invasive tools that can assess the severity of cirrhosis and risk stratify prior to decompensation is currently an unmet need. The assessment of LSM using Velacur may eventually allow for a noninvasive, immediate, objective and efficient method for estimation of disease severity in patients with cirrhosis. Moreover, assessment over time of LSM may also allow for assessment of disease progression or regression from treatment interventions. We anticipate that baseline measurements of LSM and longitudinal changes ($\Delta LSM/\Delta t$) will serve as a prognostic tool in patients with cACLD.

Hypothesis: The severity of portal hypertension in compensated advanced chronic liver disease (cACLD) can be assessed measuring LSM by Velacur.

Specific Aim 1: To examine the relationship between LSM by Velacur and the presence of esophageal or gastric varices and portal hypertensive gastropathy in patients with compensated

advanced chronic liver disease (cACLD). We will measure LSM by Velacur in this single center clinical study comprising of 200 patients with cACLD (defined by LSM ≥10 kilopascals (kPa) according to the Baveno VI recommendations) who have not had a liver transplant.

Specific Aim 2: Compare the performance of LSM by Velacur for predicting CSPH, esophageal and gastric varices to that of FibroScan® and other non-invasive markers such as MELD, CPT, platelets count, splenomegaly, APRI and FIB4.

Proposed Study Design: This is a cross sectional study that evaluates the relationship between LSM by Velacur in patients with cACLD and manifestations of portal hypertension.

Inclusion/Exclusion Criteria

Inclusion criteria:

1. Adults aged 18 years or older
2. Ability to provide informed consent
3. Diagnosis of cirrhosis based on liver biopsy, imaging, FibroScan®, or Hepatologist assessment.
4. Planned or recommendation of one of the following:
    a. standard of care upper endoscopy to screen for varices within (+/-) 6 months of the Velacur study
    b. standard of care transjugular liver biopsy with portal pressure measurement within (+/-) 6 months of the Velacur study

Exclusion criteria:

1. Inability or refusal to provide informed consent
2. Fasting for less than three hours prior to the scan
3. Subject is a pregnant or lactating female
4. Current, significant alcohol consumption
5. Subject is unable to reliably quantify alcohol consumption based upon local study physician judgment
6. Patients with a pacemaker or defibrillator
7. Acute hepatitis defined as AST/ALT > 500 U/L
8. Ascites

Screening and Enrollment

Up to 200 patients with cACLD who have not undergone liver transplantation who are seen in the liver clinics at IUH-Digestive and Liver Disorder Clinics and at Springmill Clinic will be enrolled into this prospective cross sectional study after obtaining informed consent. Standard inclusion and exclusion criteria for Velacur will be used. Patients who meet the inclusion criteria will be offered the opportunity to undergo additional testing with Velacur to measure LSM after informed consent. In addition to history and physical, we will capture pre-specified liver related findings using standardized case report forms. Participants will be enrolled over a 24 month period.

Study Procedures

At Enrollment: After subject identification, an informed consent will be obtained. All patients have to be fasting for at least three hours prior to performance of the study. Velacur exam will be performed by a Velacur certified technician. Duration of participation for the subject should be no more than one hour. Medical information from the subjects, including results of the scans, historical laboratory and diagnostic testing data will be obtained from medical records and will be entered into a database. Laboratory data for calculating non-invasive markers such as MELD, CPT, platelets count, splenomegaly, APRI and FIB4 will be collected from standard of care labs done within 6 months of the endoscopy or portal pressure measurement by transjugular liver biopsy.

Reporting of Adverse Events or Unanticipated Problems Involving Risk to Participants or Others

The Division of Gastroenterology/Hepatology at IUSM has considerable experience in the conduct of clinical studies.

Participation in this study may cause a loss of privacy. To minimize this risk, all of the patient's personal and medical data will be considered confidential to the extent allowed by law; every effort will be made to keep all of the information strictly confidential. All study information will be stored in locked cabinets and on password-protected computers. Only authorized personnel will have

access to the samples, databases, and results. When the study is published, no names or other identifying information will be used.

While there are no direct risks from use of Velacur, patients may be uncomfortable lying on their back for a brief period of time. They may experience soreness at the probe site. There is a small risk of an allergic reaction to the gel utilized during the procedure.

Patients will be closely monitored for any evidence of adverse events. Any adverse events associated with the study will be documented and the IRB will be notified per reporting guidelines.

Study Withdrawal/Discontinuation

The subject is free to withdraw from the study for any reason and at any time without giving a reason for doing so and without penalty or prejudice. The Investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

Statistical Considerations

Descriptive statistics such as mean, standard error, and percentages were used to characterize the cohort. Comparisons will be made between groups by using Student t test or analysis of variance. Pearson correlation coefficient will be used to detect the correlation between continuous variables. Multivariate analysis will be performed to examine the independent association between dependent and several independent variables. The diagnostic accuracy of LSM will be calculated using area under the receiver operator curve analysis. Sample size is based on clinical experience and precedent established for studies of similar design.

Privacy/Confidentiality Issues

Participation in this study may cause a loss of privacy. To minimize this risk, all of the patient's personal and medical data will be considered confidential to the extent allowed by law; every effort will be made to keep all of the information strictly confidential. All study information will be stored in locked cabinets and on password-protected computers. Only authorized personnel will have access to the samples, databases, and results. Samples will be labeled with a code. When the study is published, no names or other identifying information will be used.

Follow-up and Record Retention

Use of Velacur is an additional tool for diagnostic purposes and provides physicians with additional clinical information to optimize patient care. No direct follow-up with participants is planned. However, the patients may be approached for repeat study and with informed consent may be enrolled again to measure any changes in the LSM and SS that may occur over time. Study records and documents will be maintained in accordance with federal, state, and university laws.

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