# Clinical Study Protocol

# Validation of Baveno VII criteria and spleen stiffness measurement on outcome prediction in patients with hepatocellular carcinoma

**Short title: BASS_HCC study**

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# 1. BACKGROUND

## 1.1 Significance of chronic liver disease and hepatocellular carcinoma

Hepatocellular carcinoma (HCC) burdens the global healthcare system with a drastic increase in incidence by 70% from 1990 to approximately 747,000 cases and 480,000 deaths in 2019.(1) Despite implementation of screening ultrasound in at-risk populations and advances in the treatment of HCC in recent decades, HCC remains a lethal malignancy with a median survival of less than a year.(2-4) Apart from the oncological factors, the underlying liver disease has an important impact on morbidity and mortality in patients with HCC as most HCC develop under the setting of chronic hepatic inflammation and fibrosis from patients with advanced chronic liver diseases of various aetiologies.(5, 6)

## 1.2 Non-invasive measurement of portal hypertension

In the Baveno VI consensus, the term "compensated advanced chronic liver disease" (cACLD) described spectrum of chronic liver diseases ranging from advanced liver fibrosis to compensated cirrhosis.(7) Patients with cACLD are at risk of hepatic decompensation and development of HCC, especially for those with clinically significant portal hypertension (CSPH), which is conventionally measured invasively by hepatic venous pressure gradient (HVPG).(8) The recently updated Baveno VII consensus implemented a non-invasive approach by incorporating liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) and platelet count in ruling in or out CSPH in patients with cACLD.(9) In the Baveno VII consensus and as well incorporated into the latest practice guidance on portal hypertension, LSM ≤ 15kPa and platelet count ≥ 150 x $10^9$/L rules out CSPH, whereas LSM > 25kPa, LSM 20-25kPa with platelet count <150 x $10^9$/L or LSM 15-20kPa with platelet count <110 x $10^9$/L rule in CSPH, prompting the presence of gastroesophageal varices.(10) As well in Baveno VI consensus, LSM < 20 kPa with platelet count > 150 x $10^9$/L also implies a minimal risk of high-risk varices and thus can have a screening oesophagogastroduodenoscopy (OGD) spared.(7)

The development of spleen stiffness measurement (SSM) by VCTE also revolutionised the field by demonstrating its correlation with portal pressure and CSPH.(11) Studies have shown that, by combining Baveno VII criteria with SSM, the accuracy in identifying CSPH (such as the presence of high-risk varices) was enhanced compared to adopting Baveno VII criteria alone.(12-14)

## 1.3 Unmet need 1: Conflicting data on LSM/SSM in prediction of hepatic events in HCC patients

Use of LSM and SSM in prediction of HCC recurrence was reported in a few previous studies. The studies involved a one-stop LSM and/or SSM measurements with longitudinal follow-up on the recurrence rate of HCC. For instance, high baseline LSM was shown to be a poor prognostic factor in patients with HCC receiving radiofrequency ablation, and achieving low LSM reduced HCC recurrence.(15, 16) Another prospective study involving 175 patients with HCC suitable for resection showed that SSM was the only predictor for late HCC recurrence.(17)

However, there are lack of data in the prediction of hepatic decompensation in patients with HCC. First, studies aiming to investigation on risk prediction of decompensation either excluded patients with HCC or regarded HCC as one of the study endpoints. Second, the present data available also showed conflicting results. For instance, two retrospective studies performed from our group suggested that Baveno VII criteria (*ie.* LSM by VCTE and platelet count) could accurately identify high risk varices and hepatic events in both advanced HCC and that of different Barcelona Clinic Liver Cancer (BCLC) stages.(18, 19) On the contrary, another retrospective suggested that the use of both Baveno VI or VII criteria were inaccurate in predicting the presence of high-risk varices or CSPH measured by HVPG across different stages of HCC.(20) Heterogeneity was present in the study subjects and data analysis among different studies, leading to divergent results. SSM as well was not included in these studies and that the effect of combined Baveno VII and SSM in prediction of decompensation in HCC patients is still uncertain.

## 1.4 Unmet need 2: Lack of standardisation and serial LSM/SSM measurement

Serial liver stiffness monitoring was reported for longitudinal assessment and risk estimation of hepatic events in some chronic liver diseases, notably metabolic-dysfunction associated steatotic liver disease.(21) Whether serial monitoring of LSM and SSM would have any clinical significance and prognostication on hepatic events or even HCC recurrence is not well ascertained. This is of high clinical relevance especially patients with HCC may undergo liver resection or other oncological treatments that possibly affect the residual liver volume and function.

Furthermore, studies are lacking in using spleen-dedicated module (SSM@100Hz) in measuring SSM in patients with HCC, as prior study used the liver-dedicated module (LSM@50Hz) to measure both LSM and SSM.(17) This may undermine the accuracy of the SSM results as the spleen is stiffness than the liver and the use of the LSM@50Hz module may potentially overestimate the SSM.(22) As SSM@100Hz has been shown to be a reliable and highly reproducible tool in assessing SSM,(23) there is an important need to confirm its validation in patients with HCC.

## 2. STUDY OBJECTIVES

1. We aim to test the hypothesis that serial monitoring of LSM and platelet count (*ie.* Baveno VII criteria), and SSM predicts hepatic events (including high-risk varices) in compensated patients with HCC for curative-intent treatment.
2. We aim to assess the change in Baveno VII criteria and SSM in prediction of HCC recurrence in compensated patients after curative-intent treatment for HCC.
3. We aim to validate the use 50Hz and 100Hz SSM module of VCTE in patients with compensated liver disease and HCC.
4. We aim to identify factors associated with hepatic events (including high-risk varices), HCC recurrence and mortality, with a special focus on serial LSM and SSM obtained by VCTE.

## 3. STUDY DESIGN OVERVIEW (Figure 1)

This study is a single-centre, prospective cohort study. Consecutive patients with compensated liver disease and HCC for curative-intent treatment will be invited to this study. The study follow-up duration will be five years. The study consists of two parts.

**Part 1:** We will perform VCTE with LSM and SSM and check platelet count during pre-operative assessment for patients with HCC for curative-intent treatment. At the same day, we will also perform OGD as screening for gastroesophageal varices. This part aims to establish the validity of using Baveno VII criteria and/or combined Baveno VII criteria and SSM in predicting high risk varices for patients with HCC.

**Part 2:** We will serially perform VCTE and checking platelet count at month 6 and then half-yearly after the HCC is treated. Follow-up OGD will also be performed at month 12, month 36 and month 60 post-operation, as well as if CSPH is first suggested according to the Baveno VII criteria. This part aims to establish Baveno VII criteria and/or combined Baveno VII criteria and SSM in predicting high-risk varices, hepatic decompensation, mortality and HCC recurrence, as well as to identify any factors associated with these events.

# 4. PATIENTS

Consecutive patients with HCC coming into the surgical ambulatory care centre, hepatobiliary surgical clinics, joint hepatoma clinic as well as hepatology clinics for pre-operative assessment in Prince of Wales Hospital in Hong Kong will be screened for the following eligibility criteria:

## 4.1 Inclusion criteria

- Aged 18 or above
- Known chronic liver disease(s)
- HCC for curative-intent treatment (defined by HCC diagnosed with typical radiological features or histology, and planned for surgical resection or local ablative therapy as a curative-intent treatment)

## 4.2 Exclusion criteria

- Current or history of decompensated liver cirrhosis (i.e. Child's C cirrhosis, prior decompensating events such as ascites, variceal bleeding, hepatic encephalopathy and hepatorenal syndrome)
    - Child's B cirrhosis without decompensating events is not excluded
- Past history of HCC (*ie.* The current HCC is a recurrence of priorly treated HCC or a second *de novo* HCC after previous first HCC)
- Non-primary liver tumour (such as secondary liver tumour due to metastasis from another distant primary tumour)
- History of liver transplantation or plan for liver transplantation as the modality of curative-intent HCC treatment
- Asplenism or history of splenectomy
- Contraindication to OGD (*eg.* Intestinal perforation of obstruction)

- Serious medical illness with limited life expectancy of less than 6 months
- Pregnancy
- Unable to obtain or refusal of informed consent from patient

# 5. CLINIC VISITS AND ASSESSMENTS

## 5.1 Clinical assessments

The following procedures will be performed at baseline and half-yearly post-HCC treatment until month 60:

- Documentation of medical history and new symptoms
- Documentation of details of HCC (number, size and location)
- Documentation of the presence of portal vein thrombosis
- Documentation of high-risk varices, hepatic events and their dates of occurrence (i.e., ascites, spontaneous bacterial peritonitis, variceal haemorrhage, hepatic encephalopathy, hepatorenal syndrome-acute kidney injury, HCC, liver transplantation)
- Dates and causes of death for patients who pass away between visits will be recorded
- Physical examination
- Anthropometric measurements including body weight, height, waist and hip circumferences, will be collected. Body mass index will be calculated as body weight (kg) divided by height (m) squared
- Blood pressure and pulse rate measured after a 15-minute rest
- Blood tests will include complete blood count, prothrombin time, renal function test, liver blood test (including alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transpeptidase), and alpha-fetoprotein
- Store 10 mL of clotted blood and 10 mL of EDTA blood for future genetic and biochemical research

## 5.2 Vibration-controlled transient elastography (VCTE)

LSM and SSM assessments will be carried out using VCTE (FibroScan 630 Expert, Echosens, Paris, France). Operators with a minimum of 500 examinations completed and trained according to the manufacturer's guidelines will conduct the tests.(24) Examinations will be performed at baseline, post-HCC treatment month 6 and then half-yearly till month 60. Ten measurements will be recorded each for the liver and spleen, and their median value will be used to derive the corresponding stiffness. The machine's automated probe selection tool will

determine the use of M and XL probes for LSM, while SSM will be measured by both the M or XL probes (50Hz@LSM) as well as the dedicated 100Hz probe.

LSM is considered reliable if there are ten or more valid measurements, and the interquartile range-to-median ratio of the measurements is ≤0.3. While no standardised reliability criteria exist for SSM, variability of SSM will be tracked in this study.

### 5.3 Oesophagogastroduodenoscopy (OGD)

OGD will be performed by experienced endoscopists with a minimum of 100 prior examinations, at baseline and post-HCC treatment month 12, month 36 and month 60, as well as if CSPH is first suggested according to the Baveno VII criteria.

The scope of the examination will include the oesophagus, stomach, and the first and second parts of the duodenum. The size of varices will be graded using the modified Paquet classification (grade I for varices extending just above the mucosal level; grade II for varices projecting by one-third of the luminal diameter and non-compressible upon air insufflation; and grade III for varices projecting up to 50% of the luminal diameter and in contact with each other).(25) Additionally, the location and presence of red wale markings will be documented. Those with high-risk varices, defined by varices of grade II or above, or the presence of red wale markings, will be treated by non-selective beta-blocker with carvedilol and/or endoscopic variceal ligation, as per latest international guideline suggestion.(10)

### 5.4 Follow-up

Other follow-up procedures will be considered as part of the standard of care and will be covered by local resources. These include but are unlimited to the treatment of chronic liver disease and co-morbid conditions as well as surveillance for recurrence of HCC through periodic imaging and/or alpha-fetoprotein testing. Patients will be scheduled for at least one annual visit or more frequently, as clinically indicated. At each visit, incident hepatic events and any HCC recurrence will be documented.

## 6. DATA PROCESSING AND ANALYSIS

### 6.1 Analysis datasets

**Part 1:** This analysis will include all eligible patients who meet the inclusion and exclusion criteria, and undergo VCTE and endoscopy at baseline.

**Part 2**: The analysis will include all patients who receive serial VCTE and OGD per study timeline.

## 6.2 Primary endpoint

The primary endpoint of this study is the composite of incident high-risk varices, hepatic decompensation and liver-related mortality. Hepatic decompensation is defined by the presence of ascites, variceal bleeding, overt hepatic encephalopathy or hepatorenal syndrome. Ascites is defined by compatible clinical signs and confirmed with ultrasound or paracentesis. Intraperitoneal fluid detected only by ultrasound is not considered an endpoint. Variceal bleeding will be suspected if patients are presented with haematemesis or melaena or a decrease in the haemoglobin level of at least 2 g/dL. The diagnosis is made when OGD shows one of the following features: active bleeding from a varix, a "white nipple" overlying a varix, clots overlying a varix, or varices with no other potential source of bleeding.(10) Overt hepatic encephalopathy is evidenced if there is symptom or sign compatible with West Haven criteria grade II or above.(26) Hepatorenal syndrome is diagnosed if there is an increase in serum creatinine ≥0.3 mg/dL within 48 hours or ≥50% increase in serum creatinine that is known or presumed to have occurred within the preceding seven days, after excluding hypovolemia, shock, nephrotoxic agents and structural kidney damage.(27)

## 6.3 Secondary endpoints

Secondary endpoints include:

- Development of each hepatic decompensation event
- Recurrence of HCC
- Change in hepatic function in terms of Child-Pugh and model for end-stage liver disease (MELD) scores
- Change in LSM and SSM

## 6.4 Sample size calculation

From our retrospective study from 673 patients with HCC of different BCLC stages recruited from 2013 to 2019 in Prince of Wales Hospital, 67.3% (453/673) were BCLC stage 0 and A (69 in stage 0 and 384 in stage A). The baseline LSM was 9.5-9.6kPa in these two BCLC stages.

At a median follow-up duration of 45.8 months, 127 (28.0%) of those in BCLC stage 0 (18.8%) and A (29.7%) developed hepatic events or liver-related mortality.(18) From another retrospective study on 533 patients with metabolic-dysfunction associated steatotic liver disease, 19.5% had worsening of LSM >20% from baseline, and change in LSM was the independent factor associated with hepatic decompensation (hazard ratio [HR] 1.56, $p$=0.04) and liver-related mortality (HR 1.96, $p$=0.02).(28) It is rational to believe that the HR is higher in patients with HCC with the use of composite primary endpoints. Also, the event rate will be higher in our study as incident high-risk varices are part of the composite primary endpoint. Using the Fine-Gray subdistribution regression model, assuming 30% of patients with HCC undergoing curative-intent treatment will have LSM/SSM deterioration leading to the development of the composite endpoint of high-risk varices, hepatic decompensation and liver-related mortality at a rate of 35% at 5 years, 127 patients are required to provide 80% power to detect a minimum subdistribution HR of 2.5 with 2-sided 95% confidence interval. Assuming up to 20% dropout rate, a total of **159 patients** will be required in this study.

## 6.5 Data analysis

Continuous variables were expressed in mean ± standard deviation or median (interquartile range [IQR]), as appropriate, while categorical variables were presented as number (percentage). Qualitative and quantitative differences between subgroups were analysed by chi-square or Fisher's exact tests for categorical parameters and Student's t test or Mann-Whitney test for continuous parameters, as appropriate. Qualitative and quantitative differences between ordinal subgroups were analysed by chi-squared test for linear trend or Fisher's exact tests for categorical parameters and one-way ANOVA or Kruskal-Wallis test for continuous parameters, as appropriate. Patients were followed until the occurrence of the endpoint, and censored upon the time of liver transplantation or at the end of follow-up period, whichever occurs earlier. Patients who withdraw consent will be censored assuming no endpoints developed after the last documented clinic visit. The primary and secondary endpoints will be analysed as time-to-event variables with hazard ratio and 95% confidence interval (CI) calculated. Event rates of endpoints will be compared with stratified log-rank test. Survival will be estimated by Kaplan-Meier method. Non-liver related mortality is considered a competing risk for the primary endpoint.

The accuracy of Baveno VII and/or SSM models in predicting high-risk varices and hepatic decompensation will be evaluated using the area under the receiver-operating characteristic curve with corresponding 95% CI. The corresponding sensitivity, specificity, positive predictive value and negative predictive value will be calculated. Multivariable logistic regression model will be performed to identify independent factors associated with hepatic decompensation and recurrence of HCC. All statistical tests are two-sided with p-value <0.05 indicating statistical significance. As patients may be started on NSBB or receive endoscopic variceal ligation during the study, a subgroup analysis will be performed for those who do not receive these treatments. Use of NSBB and prior endoscopic variceal ligation are also included as covariates in the multivariable analysis.

We hypothesise that non-invasive tests could detect hepatic decompensation, CSPH and recurrence of HCC at earlier timepoints. Therefore, we will examine baseline and follow-up LSM, SSM, platelet count, and their combinations, together with baseline demographics, liver biochemistry and baseline characteristics of HCC as potential predictors of these endpoints.

### 6.6 Anticipated challenges and contingency plans

Our team possesses the expertise and track records required to execute this study successfully. In case of challenges in recruitment, we have plans to invite other local centres for case referral as well as to include collaborating sites. Currently, our university is leading a multicentre randomised controlled trial on the use of carvedilol in treating patients with CSPH with participating sites in Malaysia and France. There is potential to expand the proposed project and accelerate enrolment.

Endoscopy is an invasive procedure. Based on our previous clinical trials , a small percentage (typically <5%) of patients may decline the follow-up endoscopy. These patients will still be included in the analysis as described above, ensuring that their data continues to contribute to the study's findings.

## 7. ETHICS

### 7.1 Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favourable opinion in writing by our Joint CUHK-NTEC CREC. The

protocol must be re-approved by our Joint CUHK-NTEC CREC annually. All subsequent protocol amendments must be approved by the CREC.

### 7.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and our Joint CUHK-NTEC CREC. This study is designed based on a thorough knowledge of the scientific background, a careful assessment of risks and benefits, have a reasonable likelihood of benefit to the population studied and will be conducted by suitably trained investigators using approved protocol.

### 7.3 Written informed consent

The investigator(s) will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The informed consent forms are available in both English and Chinese. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allow time to consider the information provided. The subject's signed and dated informed consent must be obtained before conducting any procedure specific for the study. The Principal Investigator must store the original, signed Informed Consent Form. One copy of the signed Informed Consent Form must be given to the subject. If modifications are made according to local requirements, the new version has to be approved by our Joint CUHK-NTEC CREC.

### 7.4 Data sharing

In line with current international standard of accountability and transparent reporting, data from this study may be shared with outside parties upon reasonable request. Care will be taken to remove sensitive data (name, identity numbers and dates of birth) before data sharing.

## 8. POSSIBLE RISKS AND ADVERSE EVENT REPORTING

### 8.1 Possible risks and discomfort

There is minimal discomfort in blood taking and undergoing VCTE. Major complications of OGD include bleeding and perforation but the major complication rate is overall less than 0.1%.

The adverse event reporting period for this study is from signing the informed consent through 30 days after the last follow-up visit.

## 8.2 Adverse event

An adverse event is any undesirable medical event occurring in the subject within the trial period, whether or not it is related to the study intervention.

The severity of an adverse event is defined as:
Mild: Transient symptoms, no interference with the subject's daily activities
Moderate: Marked symptoms, moderate interference with the subject's daily activities
Severe: Severe interference with the subject's daily activities.

The relationship of an adverse event to the study intervention is defined as:
Probable: Good reasons and sufficient documentation to assume a causal relationship
Possible: A causal relationship is conceivable and cannot be dismissed
Unlikely: The event is unlikely related to the study intervention

A telephone enquiry hotline for reporting subject's adverse events is available. The investigator will record all relevant information including signs and symptoms of the event, the onset time, the date of the event, the laboratory findings, concomitant drugs, and the outcome. All adverse events will be followed up until we have reached a defined outcome of the event, which can be one of the followings: (1) recovered with sequelae (for chronic conditions), (2) recovered, or (3) the management of the adverse event is taken over by another physician when the study ends.

A clinical laboratory adverse event is any clinical laboratory abnormality that suggests a disease and/or organ toxicity is of sufficient severity that requires active intervention (i.e. change of dose, discontinuation of drug, more frequent follow-up or further investigation). An unscheduled visit will be performed if subjects have to withdraw early from the study.

## 8.3 Serious adverse events

A serious adverse event is an adverse event that results in one of the following outcomes:

- Death

- Life-threatening
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect

The definitions of causal relationship to study intervention are the same as those for adverse events. We have a 24-hour on-call system to handle serious adverse events. The investigator will assess and treat the subjects as soon as possible. A standard serious adverse event form will be used (provided by the CREC at http://intranet.ccter.cuhk.edu.hk/sae/) to report the events within 24 hours after acknowledgement. We will arrange unscheduled follow-up visits immediately or within 24 hours on receiving the subject's self-report of serious adverse events after the subjects have been discharged or if the subject has already been admitted to the hospital. Our investigators will assess the subject within 24 hours. The study team will record all relevant information including signs and symptoms of the event, the onset time, the date of the event, the laboratory findings, concomitant drugs, and the final outcome. A follow-up serious adverse event form will be sent within 14 days after submitting the initial serious adverse event form. Serious adverse events related to the study drug will be followed up until the subject has "recovered", "recovered with sequelae" or "died". SAE reports will be sent to our ethics committee. An unscheduled visit will be performed if subjects have to withdraw early from the study.

### 8.4 Emergency contact person

Dr. Jimmy Che-To Lai (Principal investigator)

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## 9. REFERENCES

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Figure 1. Study design overview and study aims. (A) 159 patients with compensated liver disease and hepatocellular carcinoma (HCC) planning for curative treatment will undergo clinical assessment and blood tests, vibration-controlled transient elastography (VCTE) and oesophagogastroduodenoscopy (OGD). The current funding exercise will cover assessments at baseline and year 1, and we will obtain future funding for assessment at subsequent years. (B) We aim to validate serial monitoring of liver stiffness measurement (LSM) and platelet count (*ie*. Baveno VII criteria), and spleen stiffness measurement (SSM) in prediction of hepatic events (including high-risk varices) in compensated patients with HCC planning for curative treatment. (C) We also aim to determine whether serial monitoring of Baveno VII criteria and SSM predicts HCC recurrence. (D) Performance of 50Hz and 100Hz SSM module of VCTE will also be validated. (E) Finally, we will identify factors associated with hepatic events, HCC recurrence and mortality.