STUDY PROTOCOL

PROTOCOL TITLE:
Predictors of decompensation, acute-on-chronic liver failure and mortality in liver cirrhosis – a multicentre, prospective, observational study from the SingHealth Chronic Liver Disease Registry (SoLiDaRity-DAM)

PROTOCOL VERSION: Version 2.1
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Table of Contents

1. BACKGROUND AND RATIONALE 3

2. HYPOTHESIS AND OBJECTIVES 5

3. EXPECTED RIKS AND BENEFITS 6

4. STUDY POPULATION 7

4.1. LIST THE NUMBER AND NATURE OF SUBJECTS TO BE ENROLLED. 7

4.2. CRITERIA FOR RECRUITMENT AND RECRUITMENT PROCESS 7

4.3. INCLUSION CRITERIA 7

4.4. EXCLUSION CRITERIA 7

5. STUDY DESIGN AND PROCEDURES/METHODOLOGY 8

6. SAFETY MEASUREMENTS 8

6.1. DEFINITIONS 8

6.2. COLLECTING, RECORDING AND REPORTING OF SERIOUS ADVERSE EVENTS (SAES) TO CIRB 8

6.3. SAFETY MONITORING PLAN 9

6.4. COMPLAINT HANDLING 9

7. DATA ANALYSIS 9

7.1. DATA QUALITY ASSURANCE 9

7.2. DATA ENTRY AND STORAGE 9

8. SAMPLE SIZE AND STATISTICAL METHODS 9

8.1. DETERMINATION OF SAMPLE SIZE 9

8.2. STATISTICAL AND ANALYTICAL PLANS 9

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS 10

10. QUALITY CONTROL AND QUALITY ASSURANCE 10

11. ETHICAL CONSIDERATIONS 10

11.1. INFORMED CONSENT 10

11.2. CONFIDENTIALITY OF DATA AND PATIENT RECORDS 11

12. PUBLICATIONS 11

13. RETENTION OF STUDY DOCUMENTS 11

14. FUNDING AND INSURANCE 11

LIST OF ATTACHMENTS 12

PROTOCOL SIGNATURE PAGE

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Predictors of decompensation, acute-on-chronic liver failure (ACLF) and mortality in liver cirrhosis – a multicentre, prospective, observational study from the SingHealth Chronic Liver Disease Registry (SoLiDaRity-DAM)

Protocol Version/ Date: Version 2.1 (7 July 2025)

Sponsor Name: SingHealth SoLiDaRity Workgroup

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described study in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator Name: Jason Chang Pik Eu

Principal Investigator Signature:

Date:

1. BACKGROUND AND RATIONALE

General Introduction:

Chronic liver disease and its ensuing complications are a significant health issue in Singapore. In the Singapore Burden of Disease Survey, liver cirrhosis and liver cancer contributed 0.9% and 3.2% respectively out of 182,753 years of life lost (1). The natural history of liver cirrhosis is characterized by an asymptomatic "compensated" phase, followed by a rapidly progressive "decompensated" phase characterized by ascites, variceal bleeding, hepatic encephalopathy, and/or jaundice. Liver decompensation occurs at a rate of 5-7% per year and is a watershed event in the natural history of liver cirrhosis as the medial survival falls from more than 12 years for compensated cirrhosis to less than 2 years in decompensated cirrhosis (2). Accurate and timely prediction of decompensation will allow pre-emptive management strategies to prevent or delay decompensation, timely intervention to treat decompensation events to ensure optimal outcome and avoid early mortality, early referral to liver transplant, and allocation of resources to optimize value-based provision of evidenced-based care.

Cirrhotic patients who require hospitalization for acute decompensation are at high risk of developing acute-on-chronic liver failure (ACLF) which is characterized by the development of organ failure and is associated with high rates of mortality (3). The ability to identify clinical predictors of decompensation, ACLF and mortality in the natural history of patients with liver cirrhosis is important as it may allow early intervention and potentially reduce the mortality rate. The PREDICT study identified three distinct clinical courses of acute decompensation – ACLF, unstable decompensated cirrhosis and stable decompensated cirrhosis, of which those with ACLF had a very high 3-month mortality of 53.7% (4). This group also identified four distinct clinical events that predicted increased 90-day mortality in acutely decompensated cirrhotics. However, there is a lack of data regarding predictors for decompensation, ACLF and mortality in patients with compensated cirrhosis. Furthermore, there is no local or Asian data validating the findings of PREDICT study regarding the progression and predictive factors for future decompensating events.

In a recent review of the existing literature (5), the most frequent predictors of decompensation were liver function, portal hypertension and indicators of inflammation/fibrosis. The impact of underlying etiology and treatment of liver disease was also a relevant predictor. This is highly relevant in the local context as most of the studies conducted in the West involve alcohol as the main etiology of cirrhosis whereas viral and metabolic hepatitis are the main etiologies of cirrhosis in our local population (6). Potential areas of research interest include the role of non-invasive markers of inflammation and fibrosis as predictors of decompensation.

In Singapore where the rates of liver transplantation remain low (7), liver cirrhosis remains an important cause of mortality. There is thus a pressing need to identify predictors of decompensation, ACLF and mortality in the natural history of liver cirrhosis in our local population. This would allow pre-emptive management to prevent or delay decompensation and early referral for liver transplantation to reduce morbidity, mortality, and healthcare burden from liver cirrhosis.

The SOLIDARITY-DAM study is a prospective, multicenter, observational study of consecutive patients with liver cirrhosis (defined as compensated advanced chronic liver disease (cACLD), compensated cirrhosis and decompensated cirrhosis) to identify clinical predictors for decompensation, ACLF and mortality.

1.2 Rationale and Justification for the Study:

There is a lack of data and understanding of the various predictive factors associated with decompensation, ACLF and death in patients with compensated cirrhosis, specifically in the local context where the primary etiology of cirrhosis is different from the West. This study aims to fill this knowledge gap.

1.2.1 Rationale for Study Population:

As the aim of the study is to find the predictive factors associated with decompensation, ACLF and death in patients with cirrhosis, all patients with cirrhosis will be offered inclusion in the study.

1.2.4 Rationale for Study Design:

This is a prospective multi-centre observational study which will involve the collection of routine demographic, clinical, biochemical, radiological and treatment data that are related to the routine management of patients with liver cirrhosis in Singapore, with a focus on identifying predictors for key clinical end-points of decompensation, ACLF and death.

2. HYPOTHESIS AND OBJECTIVES

2.1 Hypothesis:

As this study is designed as a prospective observational study, we do not have an a-priori mechanistic or pathophysiological hypothesis. We hypothesize that through this study, we will be able to identify clinical, biochemical and/or radiological predictors for development of decompensation, ACLF and mortality in patients with cirrhosis.

2.2 Primary Objectives:

The primary aim of this study is to prospectively identify factors that predict decompensation, ACLF and death in patients with cirrhosis.

Specific goals of the study:

- To study the 1-, 3- and 5-year risk of decompensation, ACLF and death in patients with compensated and decompensated liver cirrhosis in Singapore

- To identify clinically relevant point-in-time predictors and biomarkers for liver decompensation in general, and for specific liver-related events (including variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, portal vein thrombosis, portopulmonary hypertension, hepatopulmonary syndrome, cirrhotic cardiomyopathy, hepatorenal syndrome, refractory ascites, sarcopenia, and liver cancer)

- To study the impact of underlying etiology of liver disease on the rate of decompensation, ACLF and death in liver cirrhosis

- To provide external validation of predictive scores for decompensation (ALBI, CHESS-ALARM, LSPS, PREDICT, etc).

- To serve as a core (hub) study for prospective ancillary studies regarding diagnosis, prognosis, and pathogenesis of AD and ACLF. These involve the following sub-goals:
    - To uncover mechanistic and pathophysiological processes associated with the development and clinical course of ACLF and to identify the precipitating events of ACLF.
    - To study the role of sarcopenia and neutrophil-lymphocyte ratio (NLR) in the development of acute decompensation, ACLF and death.
    - To predict the response to NSBB based on the blood biomarkers (ie, Neutrophil to lymphocyte ratio, Lymphocyte to monocyte ratio).
    - To develop an AI model of diagnosis of Sarcopenia and clinically significant portal hypertension based on Computerized Tomography (CT) imaging.

- To develop a score predicting ACLF development and assess 28-day, 90-day, 6-month and 1-year all-cause mortality in cirrhotic patients with acute AD, but without ACLF.

Any ancillary studies which require additional collection of biosamples and/or interventions (e.g. CT scans) which are not part of standard-of-care management will require separate informed consent to be obtained from the study participants.

If the initial results of our study are positive, we intend to request for an extension of the study to 10 years to evaluate the 10-year risk of decompensation, ACLF and death as well as the effect of potential interventions on these risks.

3. EXPECTED RIKS AND BENEFITS

As this study is a prospective observational study, there are no distinct clinical risks to patients.

There may be the potential risk of breach of confidentiality since patients' medical records will be assessed for purposes of the study. Measures to mitigate these risks include:

(i) restricting RedCap access to study team members only. This will prevent other non-authorized individuals from accessing patient data

(ii) restricting RedCap access to specific institutions. This will prevent investigators from accessing data of patients from other hospitals. Investigators will only be able to access the data of participants from their own institutions.

(iii) anonymizing data that will be pooled for analysis.

The benefit to recruited patients include better understanding of the disease condition and initiation of treatments based on study results.

4. STUDY POPULATION

1. This multicenter study aims to recruit 2,200 (two thousand two hundred) cirrhotic patients over a 5 (five) year period from 3 institutions in SingHealth – Changi General Hospital (CGH), Sengkang General Hospital (SKH) and Singapore General Hospital (SGH).

2. Patients will be recruited both from the inpatient and outpatient setting. All consecutive patients admitted/referred to the study center with a clinical diagnosis of liver cirrhosis (based on standard clinical, radiological, elastography and/or histological criteria) will be offered inclusion into the SoLiDaRity-DAM study.

3. After the enrolment all patients will be followed up till liver transplantation or death.

4. Demographic, clinical, biochemical, pharmacological and other specialized investigational data (done as per routine care) will be collected and stored in an electronic database in RedCap.

5. Specific end-points of the study will include decompensation, ACLF and death.

6. Prospective collection of biological material as part of routine standard of care and performance of ancillary studies investigating predictors for development and pathogenesis of ACLF may be carried out may be carried out with the expressed consent of study participants.

4.1. List the number and nature of subjects to be enrolled.

1. Total Number of Subjects/Patients: 2200
2. Nature of Patients: Patients with compensated or decompensated Cirrhosis from 3 participating sites, namely CGH, SKGH and SGH.

4.2. Criteria for Recruitment and Recruitment Process

Patients with a clinical diagnosis of cirrhosis will be offered inclusion into the study.

4.3. Inclusion Criteria

1) Patients with clinical diagnosis of liver cirrhosis (radiological evidence of cirrhosis on ultrasound, CT and/or MRI liver, and/or liver stiffness > 10kPa or equivalent, and/or histology compatible with liver cirrhosis)
2) Age 18 years and above (parental consent required if below 21 years)
3) Willing and able to provide informed consent

4.4. Exclusion Criteria

1) No clinical evidence of liver cirrhosis
2) Less than 18 years of age
3) Declined or unable to provide informed consent to participate in study

5. STUDY DESIGN AND PROCEDURES/METHODOLOGY

The design of the study is a prospective observational, with the aims of understanding the factors associated with decompensation, ACLF and Death in patients with cirrhosis. Special focus areas are the critical period prior to the development of ACLF, to uncover mechanistic and pathophysiological processes associated with the development and clinical course of ACLF and to identify the precipitating events of ACLF.

6. SAFETY MEASUREMENTS

6.1. Definitions

Serious adverse event (SAE) in relation to human biomedical research, means any untoward medical occurrence as a result of any human biomedical research which:

- results in or contributes to death
- is life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in or contributes to persistent or significant disability/incapacity or
- results in or contributes to a congenital anomaly/birth defect
- results in such other events as may be prescribed

Adverse event (AE) in relation to human biomedical research means any untoward medical occurrence as a result of any human biomedical research which is NOT serious. Adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease possibly/ probably/ definitely associated with the participant in the human biomedical research.

6.2. Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to CIRB

Only related SAEs (definitely/ probably/ possibly) will be reported to CIRB. Related means there is a reasonable possibility that the event may have been caused by participation in the research. Please refer to the CIRB website for more information on Reporting Requirement and Timeline for Serious Adverse Events.

The investigator is responsible for informing CIRB after first knowledge that the case qualifies for reporting. Follow-up information will be actively sought and submitted as it becomes available.

Related AEs will not be reported to CIRB. However, the investigator is responsible to keep record of such AEs cases at the Study Site File.

6.3. Safety Monitoring Plan

Patients participating in the study will be offered enrolment for ancillary interventional studies as and when required. A separate protocol amendment for the ancillary interventional study will be submitted in case there are ancillary studies planned.

Data collected from the study will be kept in a password-protected computer in a locked room. Where transfer of video clips is required, a hard drive with industry level encryption will be used. The Principal Investigator and co-investigators mentioned will have access to the data, which will not be made available to other personnel to protect the confidentiality of participants.

6.4. Complaint Handling

Any complaint made by participants in relation to the study will be handled as per routine clinical practice. We do not anticipate complaints peculiar to the study as it is non-invasive, non-interventional.

7. DATA ANALYSIS

7.1. Data Quality Assurance

The investigators in this study will undergo site visit initiation and be required to familiarise themselves with the study protocol. In addition, data collection will take place using a standard template to ensure accuracy and consistency of data.

7.2. Data Entry and Storage

Data will be entered and kept in RedCap.

8. SAMPLE SIZE AND STATISTICAL METHODS

8.1. Determination of Sample Size

We aim to recruit a total of 2200 patients over 5 years for this study.

8.2. Statistical and Analytical Plans

a. General Considerations: Standard statistical tools will be used for data analysis.

b. Safety Analyses: This is not applicable in the study as there will be no intervention arm.

c. Interim Analyses; will be carried out at the completion of 1, 3 and 5 years of patient recruitment

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The Principal and Co-investigators, together with the study co-ordinator, will ensure completeness of data and quality assurance. In addition, as the data will be collected in RedCap, the use of mandatory fields will add further to the quality assurance for the study.

11. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final Study Protocol, including the final version of the Participant Information and Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB), prior to enrolment of any patient into the study.

The principal investigator is responsible for informing the CIRB of any amendments to the protocol or other study-related documents, as per local requirement.

11.1. Informed Consent

Participants who present to the Department of Gastroenterology and Hepatology, Changi General Hospital, Sengkang General Hospital or Singapore General Hospital with clinical diagnosis of cirrhosis will be offered enrolment into the study. Informed consent will be obtained in the presence of a witness who is 18 years of age or older and has mental capacity. The witness will be present during the entire informed consent discussion and will not be the same person taking consent. The witness may be a member of the study team. Informed consent will be taken in the presence of impartial witness who are independent form the study if the participant is unable to read and/or sign and date on the consent form (i.e., using participant or legal representative thumbprint). If the patient is below 21 years of age, parental consent will be required.

Participant/ legal representative who do not understand English well will have the informed consent form translated by the study team, a family member or clinic staff. The participant will be informed of the study process in a language or dialect that is understood by them, and translator information will be documented in the informed consent form under the section of "Translator information". Translation will be done in the presence of impartial witness during the informed consent process.

11.2. Confidentiality of Data and Patient Records

Data collected from the study will be kept on an encrypted file in a password-protected computer in a locked office. The Principal Investigator, co-investigator and study co-ordinator will have access to the data, which will not be made available to other personnel to protect the confidentiality of participants.

RedCap access for this study will be limited to the Principal Investigator, Co-investigators, and the study co-ordinator.

12. PUBLICATIONS

The study findings will be published in peer-reviewed journals at the discretion of the Principal and co-investigator. The authorship will be based on the following 4 criteria: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work in accordance to ICMJE recommendations. All contributors who do not meet the criteria for authorship will be listed in acknowledgement section. The manuscript will be reviewed and approved by all authors prior to submission. In the event of any publication regarding the Study, the identity of the subjects will remain confidential.

13. RETENTION OF STUDY DOCUMENTS

Records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.) as well as IRB records and other regulatory documentation will be retained by the PI electronically in a secure storage facility. The records will be accessible for inspection and copying by authorized authorities. Research data will be retained in a secured storage facility for a minimum of 6 years after completion of research study or date of publication of the research using the research data, whichever is later.

14. FUNDING and INSURANCE

The logistics for the study is funded by the Transplant Centre, SingHealth. Other than that, there is no other anticipated funding needs for the study. As and when ancillary studies are planned, funding needs will be reassessed and the study can be funded via local or international research grants.

List of Attachments

Appendix 1 References

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3. Moreau R, et al, CANONIC Study Investigators of the EASL–CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013 Jun;144(7):1426-37, 1437
4. Trebicka J, et al; PREDICT STUDY group of the EASL-CLIF Consortium. The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology. J Hepatol. 2020 Oct;73(4):842-854
5. D'Amico G, Perricone, G. Prediction of decompensation in patients with compensated cirrhosis: does etiology matter? Current Hepatology Reports June 2019;18(1):1-13
6. Chang PE, Wong GW, Li JW, Lui HF, Chow WC, Tan CK. Epidemiology and Clinical Evolution of Liver Cirrhosis in Singapore. Ann Acad Med Singap. 2015 Jun;44(6):218-25
7. Tan EK, Goh BKP, Lee SY, Krishnamoorthy TL, Tan CK, Jeyaraj PR. Liver Transplant Waitlist Outcomes and the Allocation of Hepatocellular Carcinoma Model for End-Stage Liver Disease Exception Points at a Low-Volume Center. Transplant Proc. 2018 Dec;50(10):3564-3570

Appendix 2

SoLiDaRity-DAM Data Collection Fields

Baseline data to be collected at enrolment

Demographics	NRIC, Name, Ethnicity, Gender, DOB, BMI
Co-morbids	DM, dyslipidemia, CCF, CKD, etc
Clinical	Diagnosis, Etiology
Biochemical	LFT, PT/INR, FBC, AFP, RP
Radiological	US, CT, MRI
Elastography	LSM, SWE, MRE
Histology	Liver biopsy
Physical exam	Ascites, encephalopathy, jaundice
Severity	Childs score, MELD
Medications	NSBB, diuretics, treatment of underlying disorder
Endoscopy	OGD findings
Interventions	HVPG, RFA, TACE, Y90
Nutrition	

Interval data to be collected during course of study (every 6 months)

Biochemical	LFT, PT/INR, FBC, AFP, RP
Radiological	US, CT, MRI
Elastography	LSM, SWE, MRE
Histology	Liver biopsy
Physical exam	Ascites, encephalopathy, jaundice
Severity	Childs score, MELD
Medications	NSBB, diuretics, treatment of underlying disorder
Endoscopy	OGD findings
Interventions	HVPG, RFA, TACE, Y90
Nutrition	BMI, HGS,
Admissions	
Complications	Ascites, variceal bleeding, encephalopathy, spontaneous bacterial peritonitis, portal vein thrombosis, portopulmonary hypertension, hepatopulmonary syndrome, cirrhotic cardiomyopathy, hepatorenal syndrome, refractory ascites, sarcopenia, liver cancer, ACLF
Death	Cause of death (liver-related or non-liver-related)

Outcome data to be collected at pre-specified analysis time-points

Decompensation	Type, frequency and outcome of decompensation episodes
ACLF	Outcome of ACLF
Death	Cause of death (liver-related or non-liver-related)