Load Incorporating Cardiac Assessment by Echocardiography In Patients with SEpsis: a Prospective Observational Study (LIAISE study)

criticalcare
RESEARCH GROUP

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

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Contents

List of abbreviations

APACHE Acute Physiology and Chronic Health Evaluation
AST Aspartate aminotransferase
BP Blood pressure
CABG Coronary artery bypass grafting
CCB Calcium channel blocker
CO Cardiac output
CPR Cardiopulmonary resuscitation
CRT Cardiac resynchronization therapy
CVP Central venous pressure
DBP Diastolic blood pressure
ECMO Extracorporeal membrane oxygenation
EF Ejection fraction
GLS Global longitudinal strain
HF Heart failure
HR Heart rate
IABP Intra-aortic balloon pump
ICD Intracardiac defibrillator
ICU Intensive care unit
LV Left ventricle
MACE Major adverse cardiac events
MCS Mechanical circulatory support
MRA Mineralocorticoid receptor antagonist
PA Pulmonary artery
PASP Pulmonary artery systolic pressure
PC Pressure control mode
PCI Percutaneous coronary intervention
PCT Procalcitonin
PEEP Positive end-expiratory pressure
P-V Pressure-volume
PSL Pressure-strain loop
PSP Pressure strain product
PVL Pressure-volume loop
QMH Queen Mary Hospital
RAASi Renin-angiotensin-aldosterone system inhibitor
RPM Revolutions per minute
RV Right ventricle
SBP Systolic blood pressure
SOFA Sequential [Sepsis-related] Organ Failure Assessment score

STE Speckle-tracking echocardiography
SVR Systemic vascular resistance
SWI Stroke work index
TAPSE Tricuspid annular plane systolic excursion
TPCH The Prince Charles Hospital
TTE Transthoracic echocardiography
VAD Ventricular assist device
VF Ventricular fibrillation
VTI Velocity-time integral
VT Ventricular tachycardia
2ch 2-chamber view (echocardiography)
3ch 3-chamber view (echocardiography)
4ch 4-chamber view (echocardiography)

1.0 SYNOPSIS

Background	Sepsis is a global killer, whereby an infection spreads throughout the body via the bloodstream. It often leads to lethal heart damage, "septic cardiomyopathy", with mortality rates for those affected soaring above 40%. To facilitate early and appropriate intervention for damaged hearts and improve their outcomes, accurate assessment of heart function, and proper prediction of their adverse events are crucial. However, conventional cardiac assessments cannot capture heart dysfunction accurately since they have a significant limitation called "load-dependency", which means these parameters' values are affected by loading conditions on the heart, such as blood pressure and circulating blood volume. In sepsis, as these loads on the heart dramatically change minute by minute, the values of cardiac assessment also fluctuate and frequently underestimates heart damage, failing to properly predict their adverse events. To address this, novel load-incorporating echocardiographic parameters can capture heart function more accurately regardless of these hemodynamic conditions, and we have demonstrated its better predictive value in cardiogenic shock cases where loading conditions similarly fluctuate. As a next step, this study seeks to elucidate their utility in patients with sepsis.
Aims	1. To investigate if novel load-incorporating echocardiography can predict adverse events more accurately than conventional parameters in adult patients with sepsis presenting to intensive care units (ICUs). 2. To identify the most sensitive cardiac parameter to predict adverse events in sepsis, from comprehensively collected cardiac parameters along with novel-incorporating echocardiography.
Hypothesis	Load-incorporating echocardiographic parameters will be more accurate in predicting the incidence of adverse events within 30 days after ICU admission than conventional echocardiographic parameters.
Methods	*The LIAISE study* is a prospective observational study comparing the performance of load-incorporating echocardiographic parameters and conventional parameters in predicting adverse events among adult patients presenting to the ICU with sepsis. It will be conducted in hospitals in Australia, Hong Kong, South Africa, and Canada, with 199 patients recruited over 2 years. All included patients will receive an regular echocardiographic assessment and their haemodynamic parameters will be simultaneously recorded. Participants will be followed for up to 1 year after enrolment. Load incorporating parameters will be derived from regularly obtained echocardiography and haemodynamic data during offline analysis. The predictive value of cardiac parameters will be evaluated based on their statistical association with clinical outcomes.
Outcomes	*Primary outcome* The incidence of all-cause death for 30 days after ICU admission *Secondary outcomes* • Incidence of and time to all-cause death or cardiovascular readmission for 1 year after ICU admission • Incidence and duration of mechanical circulatory support, mechanical ventilation, renal replacement therapy, and vasoactive agent therapy during initial admission. • Reversibility of cardiac function (LVEF increases ≥ 5% in echo 3-5 days after ICU admission (1)) • Sequential Organ Failure Assessment (SOFA) score at 3 days after ICU admission

2.0 STUDY ADMINISTRATIVE STRUCTURE

This study will be led by the Critical Care Research Group (CCRG) at The Prince Charles Hospital (TPCH), Queensland (QLD), Australia. At each participating hospital, there will be a site principal investigator (2.3), and the site principal investigator will organize co-investigators and manage the study in each site. All major decisions will be taken by the coordinating centre (CCRG) in collaboration with the principal investigators from each site, and minor and daily decisions will be taken by the site principal investigator or the local research group.

2.1 Coordinating and Management Centre

- ✓ Critical Care Research Group, The Prince Charles Hospital, Queensland, Australia

2.1.1 Responsibilities
· Human research ethics committee applications
· Management of study budget and liaison with funding bodies
· Protocol and case report form (CRF) design and production
· Database design and management
· Protocol training of investigators, research coordinators, and the LIAISE study team
· Study set-up
· Consent form obtainment
· Coordination of data entry and feedback of data inquiries
· Monitoring and organization of investigator online meetings
· Serious adverse event notification
· Data analyses, information dissemination, and lead collaborative manuscript development

2.2 Collaborating Centres

- ✓ The Prince Charles Hospital (TPCH), QLD, Australia
- ✓ Caboolture Hospital, QLD, Australia
- ✓ Queen Mary Hospital, Hong Kong
- ✓ University of Cape Town, South Africa
- ✓ University of Toronto, Canada

2.2.1 Responsibilities:
· Approval of final protocol and data collection form
· Local ethics committee application
· General study management issues in each site
· Serious adverse event notification

2.3 Study Members

2.3.1 The Prince Charles Hospital (Australia)

Dr. Maithri Siriwardena (Site primary investigator)
Intensivist, Intensive Care Unit, TPCH, Chermside, QLD, Australia
Dr. Hideaki Nonaka (Site co-primary investigator)
PhD fellow / Cardiologist, IMB UQ, QLD, Australia
Critical Care Research Group, The Prince Charles Hospital, QLD, Australia
Dr. Ramsy Dsouza

Intensivist, The Prince Charles Hospital, QLD, Australia
Dr. Hideaki Nonaka (Site co-primary investigator)
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ICU consultant, The Prince Charles Hospital
Associate Professor, UQ, QLD, Australia
Ms. Claire Wilson
Research Nurse, Critical Care Research Group, The Prince Charles Hospital
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CCRG clinical research lead, TPCH, Chermside, QLD, Australia
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Sonographer, TPCH, Brisbane, QLD, Australia
Dr. David G Platts
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2.3.2 The University of Queensland (Australia)

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Dr. Wai Ching Sin
Intensivist, Intensive Care Unit, Queen Mary Hospital, Hong Kong
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Intensivist, Intensive Care Unit, Queen Mary Hospital, Hong Kong
Dr. Wing Sze Wincy Ng
Intensivist, Intensive Care Unit, Queen Mary Hospital, Hong Kong
Dr. Tsz Ying Kelly Lee
Intern, Queen Mary Hospital, Hong Kong
Yuk Wang Calvin Tam
Research assistant, Queen Mary Hospital, Hong Kong
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Senior research assistant, Queen Mary Hospital, Hong Kong

2.3.4 University of Cape Town (South Africa)

Dr. David Thomson (Site primary investigator)
Consultant Surgeon Transplant Unit and Critical Care Subspecialist, Cert Critical Care, South Africa
Dr. David Fredericks
Senior Specialist Emergency Medicine at Somerset Hospital Emergency Centre, South Africa
Dr. Malcolm Miller
Consultant (Anaesthesia and Perioperative Medicine, Division of Critical Care), South Africa

2.4 Statistician

Dr. Nicole White
Statistician, Queensland University of Technology, QLD, Australia
Statistician, CCRG, TPCH, QLD, Australia

2.5 Contact Details

2.5.1 Coordinating centre

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2.5.2 Contact Person of LIAISE study

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2.5.3 Coordinating Principal Investigator

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Professor, Anaesthesiology and Critical Care School of Medicine, UQ, Director of CCRG, QLD, Australia

3.0 LAY DESCRIPTION

Sepsis is a serious condition that happens in severe infection and when the body's immune system has an extreme response to an infection. It is caused by any type of infection including bacteria, viruses, parasites, or fungi, and the infection itself and body's excessive reactions can cause damage to every organ. Starting with fever, confusion, and body pain, sepsis ultimately leads to shock (low blood pressure), multiple organ failure, and death.

Septic cardiomyopathy (SC) is an injury to the heart caused by this overwhelming infection, which frequently worsen the patients' condition, causing severe shock and oedema, increasing their death rate up to 40%. The primary reason for this high death rate is the difficulty in capturing heart

dysfunction properly in sepsis. Since conventional methods for heart assessment (echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI)) are significantly influenced by the "loads" on the patient's heart, such as blood pressure and circulating blood volume, any changes in these loads can influence the accuracy of conventional assessment. As these loading conditions dramatically change minute by minute in sepsis, conventional assessments cannot capture heart dysfunction properly, making heart assessment in this population very challenging. In fact, global guidelines have not determined the diagnostic criteria of SC and SC is usually therefore not detected until the patient becomes too ill for most treatments to be effective.

Our group has previously identified novel heart echocardiographic parameters that can assess heart function while taking into account the impacts of changes in blood pressure and volume, and have verified their utility in other critically ill patient populations (2,3). In this project, we aim to investigate the utility of these new parameters in patients with sepsis, aiming for accurate and timely detection of SC and accurate prediction of adverse events caused by SC.

4.0 BACKGROUND

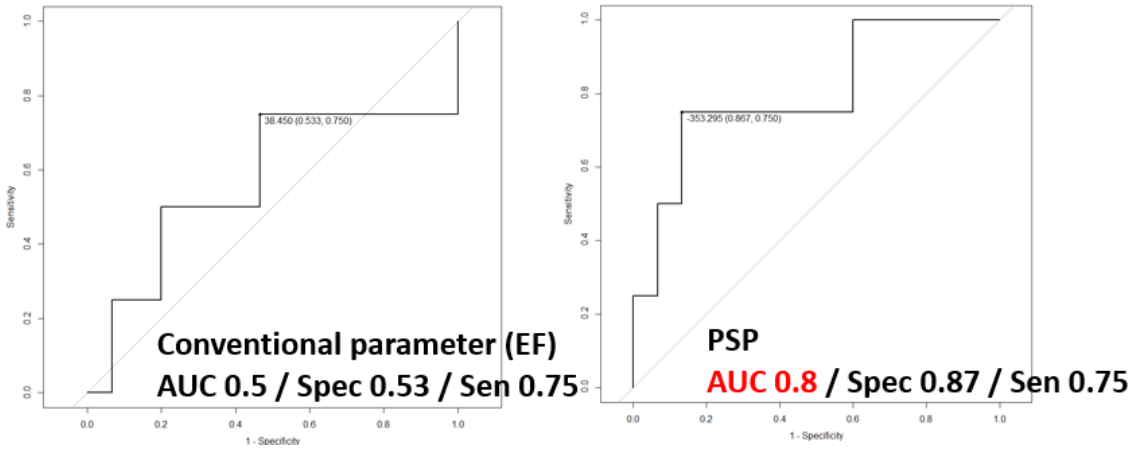
Sepsis is a severe condition frequently observed in the ICU, in which an infection spreads throughout the body via the blood, leading to multiple organ failure and poor clinical outcomes. An estimated 48.9 million incident cases of sepsis and 11.0 million sepsis-related deaths were recorded worldwide in 2017, representing 19.7% of all global deaths (4). Septic cardiomyopathy, a condition in which the heart muscle loses its ability to efficiently pump blood, occurs in 10-70% of patients with sepsis, causing mortality rates as high as 42.1%, which is three times higher than that of septic patients without SC (5,6).

One significant factor contributing to this poor clinical outcome is the difficulty in assessing left ventricle (LV) dysfunction during sepsis. Echocardiography is a non-invasive and the most frequently used tool for heart assessment in ICU settings, but conventional echocardiography assessment methods (including left ventricular ejection fraction (LVEF) and strain) have a significant limitation called "load-dependency", which means that its value fluctuates depending on the heart's loading conditions. In sepsis, the systemic inflammation reduces both pre- and after-load on the heart. Therefore, the heart gets relieved from these loads and appears to be moving well on echocardiography, with the values used for conventional assessments improving even though the heart is intrinsically injured and declines its function (7-11). This results in the delayed or missed detection of SC and subsequent refractory heart failure.

To overcome this load dependency of currently available evaluation tools and inaccurate cardiac evaluation, we have created innovative load-incorporating echocardiographic parameters. These include:

1) Pressure strain product (PSP) is one of the load-incorporating parameters, obtained by a simple formula of "**peak strain value x mean arterial pressure**". By incorporating loading condition (arterial pressure), it captures intrinsic heart function in a load-independent fashion. In our preclinical study (2,3), PSP showed excellent correlation (area under the curve (AUC): 0.80) with LV stroke work index (LVSWI), which is the gold standard for load-independent cardiac assessment (12-14). LVSWI is an invasive parameter obtained with conductance catheter in preclinical studies for detailed pathophysiological evaluation and therefore not regularly used in ICUs. In contrast, PSP can be easily obtained in clinical settings because of its non-invasive nature and it has demonstrated better predictive value for short-term outcomes in patients treated with extracorporeal membrane oxygenation (ECMO) (CASTANET study (HREC/2022/QPCH/78912); Figure 2) than conventional parameters. We hypothesise that this would also be applicable to sepsis and able to accurately capture cardiac damage in sepsis regardless of the loading conditions.

Figure 1. ROC curve analysis of LVEF and PSP for 30-day outcomes



2) Myocardial work (MW) is also a load incorporating echocardiographic parameter. This can be obtained by a complex calculation from the pressure strain loop, but can also be readily **obtained by software computation (EchoPAC 204 GE healthcare)** with only strain analysis and blood pressure input. This consists of three main components: **global work index (GWI), constructive work (CW), and wasted work (WW)**. GWI (mmHg%) is the average work performed by the entire ventricle. CW (mmHg%) and WW (mmHg%) are both regional and global measurements, representing actual regional work and inefficient work. Particularly GWI represents the load-incorporating external heart work and has demonstrated excellent sensitivity to detect diseased heart or predictive value for subsequent adverse cardiac events (15,16,17). This approach also has the potential to capture heart damage accurately in sepsis.

3) Echocardiographic pulmonary to left atrial ratio (ePLAR) is the parameter initially developed for differentiating pre-capillary and post-capillary pulmonary hypertension, as a surrogate of invasively obtained trans-pulmonary gradient pressure (18). It is calculated from **the maximum tricuspid regurgitation continuous wave Doppler velocity (m/s) divided by the transmitral E-wave: septal mitral annular Doppler Tissue Imaging e'-wave ratio (TRVmax/E:e')**. Currently, its utility has been demonstrated in COVID-19 cases and critical care settings where haemodynamic and loading conditions significantly change similar to in sepsis (19), thus potentially being useful in sepsis.

The aforementioned parameters have demonstrated excellent sensitivity to detect cardiac damage or predict subsequent adverse events in heart disease or critically ill patients, yet their data on sepsis is scarce. In the LIAISE study, we aim to investigate the prognostic benefit of these new parameters

and identify the most accurate echocardiographic parameter(s) to detect the cardiac damage and predict adverse events due to SC.

5.0 OBJECTIVES

5.1 Aims:

1. To investigate if load-incorporating echocardiography can predict adverse events more accurately than conventional echocardiograph parameters in adult patients with sepsis presenting to ICUs.
2. To identify the most sensitive cardiac parameter to predict adverse events in sepsis, from comprehensively collected cardiac parameters along with load-incorporating echocardiography.

5.2 Hypothesis:

We hypothesize that load-incorporating echocardiographic parameters will be more accurate in predicting primary outcome than conventional echocardiographic parameters.

6.0 STUDY OUTCOMES

The definition for each outcome is described in [10.5 Data variables collected]. Patient records will be accessed to collect relevant information and long-term outcomes will be determined from telephone interviews.".

6.1 Primary Outcome

The incidence of all-cause death for 30 days after ICU admission

6.2 Secondary Outcome

1. Incidence of and time to all-cause death or adverse cardiac event readmissions for 1 year after ICU admission
2. Incidence and duration (days) of mechanical circulatory support, mechanical ventilation, renal replacement therapy, and vasoactive agent therapy during initial admission
3. Reversibility of cardiac function (LVEF increases ≥ 5% in echo from 3-5 days after ICU admission (1))
4. Sequential Organ Failure Assessment (SOFA) score at 3 days after ICU admission

6.3 Tertiary Outcomes

1. ICU length of stay for primary admission
2. Hospital length of stay for primary admission
3. In-hospital mortality in primary admission
4. Vasoactive-inotropic score at 24, 48, and 72 hours
5. The amount of fluid administered for the first 24 hours in ICU admission
6. Incidence of and date of Infective endocarditis

7.0 OVERALL STUDY DESIGN

7.1 Study Design

The LIAISE study is a prospective observational study comparing load-incorporating echocardiographic parameters with conventional echocardiographic parameters for predicting adverse events in patients with sepsis presenting to the ICU. It will be conducted in hospitals in Australia, Hong-Kong, South Africa, and Canada, with 199 patients recruited over 2 years. Among patients meeting the inclusion criteria and no exclusion criteria, a regular echocardiographic assessment and their simultaneous haemodynamic condition will be recorded. Outcome data will be collected at 30 day and 1 year after ICU admission. Load-incorporating echocardiographic parameters will be analysed in offline manner with the collected echocardiography image and hemodynamic conditions. The predictive value of cardiac parameters will be assessed with receiver operating characteristic (ROC) curves, C-statistic, and multivariable analysis, in which a higher area under the curve, higher C-index, and higher hazard ratio indicate a better predictive value. These analyses will provide the general accuracy of novel parameters in outcome prediction (Aim 1) and sensitivity will be evaluated with ROC curve analysis (Aim 2).

7.2 Study Locations

- The Prince Charles Hospital (Australia)
- Caboolture Hospital (Australia)

- Queen Mary Hospital (Hong Kong)
- University of Cape Town (South Africa)
- Toronto General Hospital (Canada)

7.3 Study Population

Consecutive adult patients admitted to the ICU of participating institutions with sepsis will be screened, regardless of the primary diagnosis for admission. If the patient meet inclusion criteria and no exclusion criteria, consent will be obtained from patients or their surrogates to get permission for the use of clinical data.

7.3.1 Inclusion criteria

Patients will be eligible if ALL the following criteria are met at ICU admission:

1. Adults ≥ 18 years old.
2. Clinically suspected of defined sepsis
3. Sepsis-induced hypotension or hypoperfusion (arterial or venous blood lactate ≥2.0 mmol/L OR mean artery pressure ≤65 mmHg over 30 mins OR at least one vasoactive or inotropic agent administered).
4. At least one dose of an IV antimicrobial has been commenced.

7.3.2 Exclusion criteria

Patients will be excluded if ANY of the following apply:

1. Suspected or confirmed pregnancy.
2. Any severe concomitant diseases with limited life expectancy <30 days.

7.4 Screening Log

All patients screened against the inclusion and exclusion criteria will be entered into the screening log at each site. Those who are excluded will have all their reason/s for exclusion recorded. De-identified screening logs from each recruiting site will be forwarded to the coordinating centre at the completion of recruitment. A screening log template will be provided to each site by the coordinating centre.

7.5 Consent Form Obtainment and Patient Recruitment Strategy

We will obtain the consent form from the patient or their legally authorized representatives ("person responsible") to get permission for their clinical and echocardiography data use.

1. **Screening timing and process:** Screening will occur from hospital presentation to ICU discharge by research staff. In this project, research staff will screen ICU patients independently every morning to identify any potential candidates for the study based on the inclusion/exclusion criteria. Once a eligible candidate is identified, the research staff will make sure of primary intensivist or physician for the patient's recruitability for this study. At this point, the research staff will ensure that the patient or their family has been informed about their condition and the diagnosis of sepsis. If the patient is recruitable for this study, research staff will contact the patient or their surrogate to obtain informed consent. The research staff are dedicated solely to research activities, ensuring that the recruitment process does not interfere with any necessary clinical investigations.
   If a patient is unconscious or their surrogate is occupied with other critical meetings (e.g., discussions about surgery or therapy), we will not approach them for recruitment.
   Additionally, echocardiography is an essential examination for patients with sepsis or severe infection, as it is necessary to exclude endocarditis and cardiogenic shock. Therefore, performing

echocardiography will not negatively impact patients and will be conducted in order of necessity, as per usual clinical practice.
In summary, the only requirement for intensivists or clinical staff is to notify research staff about their recruitablity, and all recruitment processes will be handled exclusively by dedicated research personnel at each site.

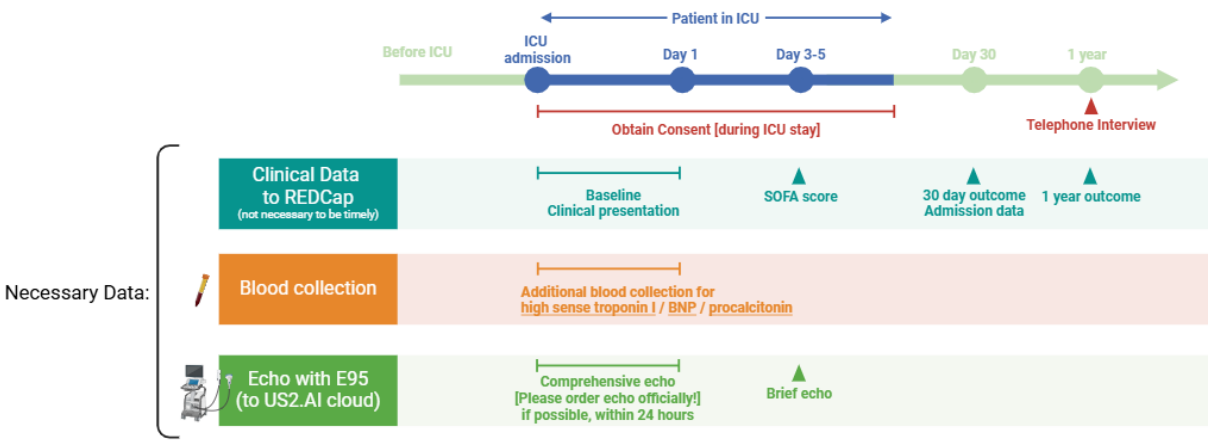
2. **Who approaches the participants:** ICU research staff
3. **How participants are initially approached:** During the participant's ICU stay, they will be approached in person by research staff after getting permission from the patient's doctors ensuring that the patient or the person responsible has been informed about their current condition and sepsis. If doctors determine that participants lack decision-making capacity, research staff will contact the person responsible in person or by telephone. Even though the consent is obtained by surrogates because patients lack of decision-making capacity, *they will be approached and have the study explained to them directly if their consciousness is restored.*
4. **Receiving recruitment documentation:** Participants will receive a patient information and consent form and a verbal explanation of the project, and if they agree to participate, will sign the consent form. This will happen during the patient's ICU stay. If the treating medical team determine that participants lack decision-making capacity, research staff will share the contents of the information and consent documents with the person responsible either in person or by telephone, and will obtain either a written or verbal consent during the patient's ICU stay. If initial consent is obtained verbally by telephone, study information and consent forms will be sent to the person responsible to sign and return, or wait until they are in ICU and give it to them. However, *If the written consent form is not received and the person responsible do not actively revoke their consents, the original phone consent will stand.*
5. **Time for consideration:** Potential participants will be given sufficient time to discuss with family, friends, and/or the treating medical team to consider whether to participate.

8.0 STUDY PROCEDURE

8.1 Study Flow

In this project, we aim to collect patients' data at the following points:

1. Before ICU admission: preadmission echocardiography for assessment before any treatment is commenced (only apical echo view and blood pressure)
2. ICU admission: clinical data collection
3. Day 1 (within 24 hours after ICU admission): Comprehensive echocardiography
4. Day 3 at ICU: SOFA score follow-up
5. Day 3 -5 at ICU: follow up echocardiography (only apical view and blood pressure)
6. (During ICU admission) Blood sampling for high-sensitive troponin I, NT-proBNP, and procalcitonin.
7. 30 days after ICU admission: outcome data collection (dead/alive, treatment details in ICU, and length of ICU/hospital stay in initial admission)
8. 1 year after ICU admission: outcome data collection (dead/alive, and details of readmission)



8.2 Echocardiography

Transthoracic echocardiography (TTE) will be performed as per standard local procedures. The echocardiography machine used for assessment must be the GE Vivid series to enable myocardial work assessment, and each echocardiogram video must be recorded with 3 beats at the minimum at a frame rate of over 40 to 90. Images will be obtained by physicians having completed their training in echocardiography or cardiac sonographers. Essential views are described in [10.5]. Recorded echocardiography data will be extracted from the machine via an external hard drive in a de-identified manner and will be uploaded to the electric database (UQ REDCap). Collected and shared data will be analysed using the load-incorporating echocardiography parameters by members from the coordinating centre having completed their training in echocardiography.

9.0 ETHICS

9.1 Ethical Conduct of the Study

This study will be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000, 2008 and Note of Clarification 2002 and 2004), and all relevant national and local guidelines on the ethical conduct of research. Ethics approval will be obtained from each participating hospital. Each site will submit the protocol and other relevant study documentation to the responsible local governance office for site-specific assessment. Approval of the protocol and related documents will be obtained prior to the start of the study. The principal investigators are responsible for ensuring that all conditions for approval of the study are met and that amendments to the protocol or serious adverse events are also reported to the ethical committees as required.

9.2 Consent from Participants

To get approval for echocardiography and clinical data use, informed consent will be obtained from patients or their legally authorized representatives (“person responsible”) in writing or through telephone as described in [7.5]. Consent can be withdrawn at any time, and in such cases, the participant's information will not be included in the study, except to report patient recruitment/retention numbers.

If verbal consent has been obtained, research staff will document that fact in the patient’s medical record.

For participants whose primary language is not English or those with literacy challenges, professional interpreter services will be used to ensure they fully understand the consent process. Culturally

appropriate and translated consent forms will also be provided where necessary. If communication barriers persist, such individuals will not be recruited to ensure ethical standards are upheld. Research staff will respect participants' cultural beliefs and practices during recruitment and discussions. To align with cultural norms, consent forms will be written in clear, accessible language, avoiding overly formal or clinical terminology. If significant communication barriers persist, or if the research staff determine that sufficient understanding cannot be ensured, such patients will not be recruited into the study.

9.3 Risk of Harm or Inconvenience Associated with This Study and Management Strategy

1. Psychological Harm: During the consent process, patients may feel anxiety or stress upon learning about sepsis and the limitations of current cardiac assessment methods. To help alleviate this, research staff, along with doctors and nurses, will provide appropriate support and counselling to minimize any psychological burden.
2. Social Harm: Although patient information is handled with the utmost care, there remains a very small risk of an inadvertent disclosure of personal information. Personal information is rigorously protected through password security, de-identification, and the use of study-specific numbering to ensure confidentiality.

9.4 Potential Benefits of Participation in This Study

1. Benefits to Participants: This study will offer participants valuable information about sepsis, heart assessment in sepsis, and the role of echocardiography as part of the consent process.
2. Benefits to Society: Insights gained from this study could enhance the understanding of sepsis, its effects on the heart, and the value of echocardiography in managing septic patients – ultimately leading to improved patient management and outcomes.
3. Potential for Broader Adoption: As echocardiography is already widely used in ICUs, positive outcomes from this research could encourage broader adoption of echocardiography in managing sepsis patients.

9.5 Justification of Waiver of Consent

The following statements justify the application for a waiver of consent:

a) Involvement in the research carries no more than low risk to participants:

a. The likelihood that harm or discomfort will occur:

i. Physical Harm: We do not anticipate any risk of physical harm.

ii. Psychological Harm: consumers may have concerns about their data being used without their consent.

iii. Devaluation of personal worth: A consumer may feel that their personhood—such as their lived experiences with mental health or identity—is reduced to mere data points, disregarding their unique story. This can lead to feelings of misrepresentation and marginalisation. Data will be handled sensitively and with respect, with the goal of benefitting future consumers.

iv. Cultural Harm: Certain cultural groups, such as First Nations people, may have specific protocols for the use of their data, and failure to respect these protocols can lead to mistrust, potentially impacting relationships with healthcare providers. 1. We will adhere to relevant Queensland Health strategies, including the HealthQ32 First Nations First Strategy 2032 which emphasises:

a. “integrated and accessible technology, digital health and analytics” to “enable information sharing across partners, access to quality data that supports holistic evidence-based decision-making, and promotes world-class First Nations health research and evaluation.” 2. Additionally, the Digital Health 2031 strategy emphasises the importance of providing digital capabilities that support

a. “equitable and accessible care closer to home for our First Nations and other diverse communities across Queensland.”

v. Social Harm: Social harm may occur if identifiable information is leaked and recognised by others, potentially affecting a consumer's social reputation, especially if the information includes sensitive healthcare data. Strict data management and governance protocols will be followed to mitigate this risk (see Section 10 for details). Data will only be accessed to personnel who are trained in confidentiality and data protection policies.

vi. Economic harm: If data are compromised and the consumer’s healthcare is impacted as a result. As mentioned above, strict data management and governance protocols will be followed

to mitigate this risk (see Section 10 for details). Data will only be accessed to personnel who are trained in confidentiality and data protection policies.

vii. Legal harm: we will seek to access identifiable patient data through a lawful disclosure pathway, obtaining approval under Chapter 6, Part 4 of the Public Health Act 2005 (QLD) via application to the Director-General of Queensland Health/ or their assigned Delegate. A waiver of consent will be sought by the HREC prior to submitting the PHA application. Approval from the Data custodian for the use of local EDIS ED data will also be requested as part of the HREC approval process.

b) The benefits from the research justify any risks of harm associated with not seeking consent – This research aligns with Every life: Queensland's Suicide Prevention Plan 2019-2029, Phase Two: "Improve the way data, evidence and evaluation is collected, used and shared to drive and improve suicide prevention", particular under Statement 45. As per National Statement (Element 4), there is social and economic value in this data in that it “is inclusive of all members of the population in question and promotes the core principle of justice.” The benefit and burdens are also spread more evenly than research based on selected participants. a. Suicide Prevention aim of this project is also “data informed”, according to the HealthQ32 strategy data-informed care can “improve access to real-time data, machine learning and artificial intelligence to gather deeper strategic insights, inform decision-making for policy, planning and service delivery, enhance productivity through autonomous systems and generate better patient outcomes”

c) It is impracticable to obtain consent – Given the large quantity of data requested, it is impractical to obtain consent from each patient. The data being requested are routinely collected as part of standard clinical care in the ED, and therefore no further data collection is required.

d) There is no known or likely reason for thinking that participants would not have consented if they had been asked – As we are analysing consumer data at a macro-level (focusing on overall patient trends rather than individual presentations), we do not anticipate consumer objections to the

retrospective analysis of their data for research aimed at improving care for individuals presenting to the ED with suicidality.

e) There is sufficient protection of their privacy – A suitable data management plan will be maintained throughout the duration of this project, to ensure suitable handling of this data (please see attachment Data Management Plan).

f) There is an adequate plan to protect the confidentiality of data - The data requested will be analysed on a macro level (i.e., examining the data overall), rather than on a micro level (i.e., we will not be analysing specific patients' data). The data will be suitably de-identified as per the eHealth De-identification and Anonymisation of Data Guidelines (please refer to Data Management Plan). See also Privacy and de-identified data from Office of the Information Commissioner Queensland.

g) In case the results have significance for the participants' welfare there is, where practicable, a plan for making information arising from the research available to them – Participants will not be contacted with results about this research. It is not expected than any incidental findings on individual participants, and their welfare, will occur.

h) The possibility of commercial exploitation of derivatives of the data or tissue will not deprive the participants of any financial benefits to which they would be entitled – This research is not expected to have potential for commercialisation. The use of this data will help the research produce exploratory models for as a prototype for prediction, rather than a commercial program.

i) The waiver is not prohibited by State, federal, or international law. – As previously mentioned, we will seek PHA approval to access the identifiable data as well as data custodian approval. Therefore, this waiver is not prohibited by state, federal, or international law.

10.0 DATA MANAGEMENT

10.1 Data Collection

Data collection will be restricted to those variables necessary to address primary, secondary, and tertiary outcomes, and define baseline participant characteristics, potential confounding co-interventions, and outcomes. All data will be collected from medical charts, echocardiography, or 1-year telephone interviews by trained research staff at each participating site. Each participant will be assigned a unique study number and only non-identifying data will be entered into the electric database (UQ REDCap) by the site research staff. The management of echocardiography data is described in [10.3]. Outcome data will be collected by research staff (via review of medical charts or telephone follow-up for discharged patients with the patient or the person responsible) 1 year after ICU admission. Before the telephone interview, research staff will first collect the clinical course information (death, readmission, and reasons of these) via medial chart.

10.2 Data Sharing Agreement

De-identified patient data will be shared only within the coordinating centre and collaborating sites. Data collected as part of this project will only be used by the study investigators listed in this protocol. For sub-analyses, permission from the coordinating principal Investigator and all site primary investigators will be required.

10.3 Offline Analysis of Shared Echocardiography Data

Obtained and de-identified echocardiographic images and videos will be extracted from each site's echo machines and uploaded to a secure, online data remittance platform. Data will be accessed by

the coordinating centre (CCRG, UQ) from this secure platform and analysed with vendor-specific offline software. Data will be analysed by an accredited echocardiologist who will be blinded to patient outcomes.

10.4 Data Management and Storage

All investigators and research staff will comply with the legislative requirements of their jurisdiction with regard to the collection, storage, processing, and disclosure of personal information. Confidentiality of all participant data will be maintained by the use of unique identifiers, password-protected electronic databases, secure storage of records, and precautions to control access to authorised personnel only. All records will be kept in compliance with each site's regulatory requirements and securely destroyed after 15 years.

10.5 Data Variables Collected

Data to be collected will include:

10.5.1 Baseline data

10.5.1.1 Screening process:

- Eligibility (whether the patient is included or not)
- Reasons for exclusion if a patient is excluded.

10.5.1.2 Patient background and demographics:

- Age
- Race (detailed race descriptions in each site are listed in the last of this part [10.5.8 Data Variables])
- Gender (male/female/other sex ascertained by medical records or self-report)
- Body weight (kg)
- Body height (cm)
- Date and time of ICU admission.
- Primary diagnosis for ICU admission (sepsis, or others (medical, surgical - elective, surgical – emergent))
- Septic shock or not (Septic shock is defined as the need for vasopressors to maintain mean arterial pressure ≥ 65 mm Hg, and a serum lactate level > 18 mg/dL [2 mmol/L] despite adequate volume resuscitation (1))
- qSOFA score (Automatic calculation)
- SOFA score at ICU admission (Automatic calculation

10.5.1.3 Co-morbidities from medical records:

- Diabetes (yes or no)
- Chronic kidney/heart diseases (yes or no, based on the patient's medical records)
- Previous LVEF (the value before sepsis or N/A)
- Previous cardiac history (coronary lesion or treatment (PCI/CABG), heart failure admission, valve surgery, heart transplantation, AF (all types), pacemaker implantation, others, or N/A)
- Performance status (fully active, slight limitation (restricted but ambulatory and able to light work), cannot work [ambulatory and capable of all self-care, but unable to work], need assistance, completely disabled): using ECOG

10.5.1.4 Clinical characteristics at ICU admission:

- Respiratory rate (bpm)
- Arterial blood pressure (SBP/DBP/mean, non-invasive measurement is acceptable)
- Heart rate (bpm)
- Altered mental status as per the Glasgow Coma Scale (for SOFA scoring)

10.5.2 Blood sampling data within 24 hours after ICU admission

- Platelet
- Total bilirubin
- Creatine
- Procalcitonin
- High-sensitive troponin T
- NT-proBNP
- PH
- PaO2

- FiO2
- Lactate (clarify from venous or artery)
- C-reactive protein

10.5.3 Echocardiographic views, and simultaneous hemodynamic parameters (within 24 hours after ICU admission)

Data and time of echo assessment
Simultaneous blood pressure (systolic/diastolic/(mean if available), non-invasive measurement is acceptable), HR, and circulatory support (device (yes or no), mechanical ventilator (yes or no), vasoactive agent (yes or no)).

1, Apical Views (for EF and strain)
  1-1, Apical Two Chamber View
  1-2, Apical Three Chamber View
    1-2-1, Pulse Wave Doppler of LVOT (for VTI, ejection time) (3ch or 5ch)
  1-3, Apical Four Chamber View
    1-3-1, Pulse wave Doppler of Mitral Inflow (for ePLAR) (4ch or 3ch)
    1-3-2, Mitral Annular Tissue Doppler Imaging e'-wave (for ePLAR)
    1-3-3, M-mode for TAPSE
    1-3-4, Continuous Wave for TPRG
  1-4, RV Focused View (for RV PSP, strain, and RV fractional area change)
2, Subcostal IVC View of Inspiratory and Expiratory (if applicable) for Estimated CVP
3, Valvular Heart Disease Greater than Moderate (If the patient has)

10.5.4 Follow-up Echocardiography (Day 3–5 in ICU)

- Date and time of echocardiography.
- Apical 2,3,4 chamber view (3 beats and 40-90 frames/s)
- Continuous wave image for TRPG and subcostal IVC view for estimated CVP
- Systemic artery pressure (systolic/diastolic) and heart rate

10.5.5 Admission data

- Suspected or confirmed site of infection (lung, blood, abdomen, soft tissue, urinary tract, central nervous system, others)
- Type of infection and organism based on blood culture (bacteria (E. coli, Klebsiella pneumonia, Staphylococcus aureus, etc.), viral, fungal, parasite, combination, unknown)
- Incidence of cardiac arrest
- Incidence and duration (days) of mechanical circulatory support (ECMO, IABP, Impella®, VAD), invasive mechanical ventilation, and renal replacement therapy during admission
- The dose (γ) at 24, 48, 72 hrs and total duration (days) of vasoactive agents (noradrenaline, adrenaline, dopamine, dobutamine, milrinone, and levocimendane for vasoactivator-inotoropes score calculation).
- The total amount (L) of fluid administered for the first 24 hours in ICU
- New onset arrhythmia (atrial fibrillation/tachycardia, ventricular fibrillation/tachycardia)
- SOFA score (automatic calculation) at Day 3-5: PaO2, FiO2, Mechanical ventilation (including CPAP), GCS, mean BP and vasoactivators, Creatinine

10.5.6 Outcome data (30 day)

- Cause and date of death
- ICU length of stay in primary admission (days)
- Hospital length of stay in primary admission (days)

10.5.7 Outcome data (1 year including after discharge)

- Cause and date of death.
- Diagnosis and date of unplanned cardiovascular readmission (ischemic heart disease, arrhythmia, stroke, cardiac arrest, valve disease, cardiomyopathy, or heart failure)
- Reason for loss of follow-up at 1 year
- Functional assessment (EQ-5D-5L)

10.5.8 Race Descriptions

Australia (Queensland):
Aboriginal
Torres Strait Islander
Aboriginal and Torres Strait Islander (Both)
White/Caucasian
East Asian (e.g., Chinese, Japanese, Korean)
South Asian (e.g., Indian, Pakistani, Bangladeshi)
Southeast Asian (e.g., Filipino, Vietnamese, Indonesian)
Middle Eastern/Arab
Pacific Islander
Black/African
Other/Multiracial

Hong Kong:
Chinese (Han majority)
East Asian (Other) (e.g., Japanese, Korean)
South Asian (e.g., Indian, Pakistani, Bangladeshi)
Southeast Asian (e.g., Filipino, Indonesian, Vietnamese)
White/Caucasian
Black/African
Middle Eastern/Arab
Other/Multiracial

South Africa (Cape Town):
Black African (e.g., Zulu, Xhosa, Sotho, Tswana)
Coloured (a widely recognized mixed-race category in South Africa)
White/Caucasian
Indian/South Asian
East Asian (e.g., Chinese, Japanese, Korean)
Southeast Asian (e.g., Filipino, Vietnamese)
Middle Eastern/Arab
Other/Multiracial

Canada:
First Nations
Inuit
Métis
White/Caucasian
Black/African Canadian
South Asian (e.g., Indian, Pakistani, Bangladeshi)
East Asian (e.g., Chinese, Japanese, Korean)
Southeast Asian (e.g., Filipino, Vietnamese, Indonesian)

Middle Eastern/Arab
Latin American
Other/Multiracial

11.0 STATISTICAL ANALYSIS

11.1 Sample Size Calculation

The proposed sample size is based on expected improvements in test sensitivity from PSP compared with LVEF by our previous study's ROC curve analysis (Figure 1), and an expected composite incidence rate of 30-day death of 20%. Our pilot study estimated that risk stratification based on LVEF ≥40% versus <40% has a sensitivity of 0.53. If PSP results in an improvement in sensitivity from 0.53 to 0.8 or higher, a sample size of 199 patients will give an expected power of 90% at the 5% level for statistical significance (two-sided alternative hypothesis) (20).

11.2 Statistical and Analytic Plan

Data are expressed as mean ± standard deviation if normally distributed, or median (interquartile range) otherwise. For the comparison of normally distributed continuous variables, a paired t-test will be used. Non-normally distributed continuous variables and ordinal varialbes will be compared with Wilcoxon signed rank test.
The agreement between intra-investigators and reliability of echocardiography analysis will be evaluated with intraclass correlation coefficient.
The predictive ability of cardiac parameters will be assessed using ROC curve analysis, C-statistic, and multivariable analysis, in which a higher area under the curve, higher C-index, and higher hazard ratio indicate a better predictive value.
Statistical analyses will be conducted using R software version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria). All P values <0.05 will be considered to indicate statistical significance.

12.0 FEASIBILITY ASSESSMENT

Based on data collected for the ARISE FLUIDS trial (Australasian Resuscitation In Sepsis Evaluation: FLUid or vasopressors In emergency Department Sepsis) at TPCH, whose inclusion criteria is almost same to this study, we anticipate the annual number of patients meeting the inclusion criteria would be 100-120 in TPCH. Considering that approximately 50% of eligible patients will be excluded because of lack of echo assessment and inappropriate image quality we expect to include 50-60 patients from TPCH annually. Furthermore, Caboolture Hospital, Queen Mary Hospital in Hong Kong, The Cape Town University in South Africa, and Toronto General Hospital in Canda also anticipate that they can recruit 60, 60, 30, 30 patients respectively over two years, thus the targeted number of patients (n=199) will be achieved in 2 years.

The project team are currently applying for relevant grants to cover relevant costs for research staff and consumables.

13.0 SUPERVISION

This project will be supervised by the co-investigators listed below, in collaboration with the coordinating principal investigator and site primary investigators.

Professor Greg Scalia
Director of the Echocardiography department at TPCH

Professor Jonathan Chan
Director of Echocardiography at the Gold Coast Heart Centre
Prof Jonathan Chan is a world-leading echocardiologist on advanced parameters such as pressure-strain product and myocardial work, that are main interests in this study. His insights are essential for study excursion and echocardiography analysis.

Dr. Jayshree Lavana
Director of Adult Intensive Care Unit at TPCH

14.0 REFERENCES

1. Mollema, Sjoerd A et al. "Viability assessment with global left ventricular longitudinal strain predicts recovery of left ventricular function after acute myocardial infarction." *Circulation. Cardiovascular imaging* vol. 3,1 (2010): 15-23. doi:10.1161/CIRCIMAGING.108.802785
2. Sato, Kei et al. "A novel speckle-tracking echocardiography parameter assessing left ventricular afterload." *European journal of clinical investigation*, e14106. 11 Oct. 2023, doi:10.1111/eci.14106
3. Sato, Kei et al. A Novel Speckle-Tracking Echocardiographic Parameter Assessing Left Ventricular Loading During VA ECMO in a Pre-clinical Model of Cardiogenic Shock. *Heart, Lung and Circulation,* VOLUME 32, SUPPLEMENT 3, S406, JULY 2023, DOI: 10.1016/j.hlc.2023.06.562
4. Rudd, Kristina E et al. "Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study." *Lancet (London, England)* vol. 395,10219 (2020): 200-211. doi:10.1016/S0140-6736(19)32989-7
5. Carbone, Federico et al. "Septic Cardiomyopathy: From Pathophysiology to the Clinical Setting." *Cells* vol. 11,18 2833. 11 Sep. 2022, doi:10.3390/cells11182833
6. Hanumanthu, Balaram Krishna J et al. "Sepsis-induced cardiomyopathy is associated with higher mortality rates in patients with sepsis." *Acute and critical care* vol. 36,3 (2021): 215-222. doi:10.4266/acc.2021.00234
7. Beesley, Sarah J et al. "Long-Term Implications of Abnormal Left Ventricular Strain During Sepsis." *Critical care medicine* vol. 49,4 (2021): e444-e453. doi:10.1097/CCM.0000000000004886
8. Ng, Pauline Yeung et al. "Speckle tracking echocardiography in patients with septic shock: a case control study (SPECKSS)." Critical care (London, England) vol. 20,1 145. 14 May. 2016, doi:10.1186/s13054-016-1327-0
9. Orde, Sam R et al. "Outcome prediction in sepsis: speckle tracking echocardiography based assessment of myocardial function." Critical care (London, England) vol. 18,4 R149. 11 Jul. 2014, doi:10.1186/cc13987
10. Burns, Andrew T et al. "Left ventricular strain and strain rate: characterization of the effect of load in human subjects." *European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology* vol. 11,3 (2010): 283-9. doi:10.1093/ejechocard/jep214
11. Beesley, Sarah J et al. "Long-Term Implications of Abnormal Left Ventricular Strain During Sepsis." *Critical care medicine* vol. 49,4 (2021): e444-e453. doi:10.1097/CCM.0000000000004886
12. Sagawa, K. "The end-systolic pressure-volume relation of the ventricle: definition, modifications and clinical use." *Circulation* vol. 63,6 (1981): 1223-7. doi:10.1161/01.cir.63.6.1223

13. Suga, H et al. “Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio.” *Circulation research* vol. 32,3 (1973): 314-22. doi:10.1161/01.res.32.3.314
14. Suga, H, and K Sagawa. “Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle.” *Circulation research* vol. 35,1 (1974): 117-26. doi:10.1161/01.res.35.1.117
15. Lustosa RP, Butcher SC, van der Bijl P, et al. Global Left Ventricular Myocardial Work Efficiency and Long-Term Prognosis in Patients After ST-Segment-Elevation Myocardial Infarction. Circ Cardiovasc Imaging. 2021;14(3):e012072. Doi:10.1161/CIRCIMAGING.120.012072
16. Chan J, Edwards NFA, Khandheria BK, et al. A new approach to assess myocardial work by non-invasive left ventricular pressure-strain relations in hypertension and dilated cardiomyopathy. Eur Heart J Cardiovasc Imaging. 2019;20(1):31-39. doi:10.1093/ehjci/jey131
17. Edwards NFA, Scalia GM, Shiino K, et al. Global Myocardial Work Is Superior to Global Longitudinal Strain to Predict Significant Coronary Artery Disease in Patients With Normal Left Ventricular Function and Wall Motion [published correction appears in J Am Soc Echocardiogr. 2020 Feb;33(2):257]. J Am Soc Echocardiogr. 2019;32(8):947-957. doi:10.1016/j.echo.2019.02.014
18. Scalia GM, Scalia IG, Kierle R, et al. ePLAR – The echocardiographic Pulmonary to Left Atrial Ratio – A novel non-invasive parameter to differentiate pre-capillary and post-capillary pulmonary hypertension. Int J Cardiol. 2016;212:379-386. Doi:10.1016/j.ijcard.2016.03.035
19. Renda G, Mennuni MG, Pizzoferrato G, et al. Predictive Value of Echocardiographic Pulmonary to Left Atrial Ratio for In-Hospital Death in Patients with COVID-19. *Diagnostics (Basel)*. 2023;13(2):224. Published 2023 Jan 7. doi:10.3390/diagnostics13020224
20. Alonzo, T.A., Pepe, M.S. and Moskowitz, C.S. (2002), Sample size calculations for comparative studies of medical tests for detecting presence of disease. Statist. Med., 21: 835-852. https://doi.org/10.1002/sim.105