COVID-19 Critical Care Consortium
Cardiac substudy protocol ver.1

A global multicenter international study evaluating the prevalence and nature of cardiac complications in critically ill COVID-19 patients

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Cardiac Sub-study Research Group (alphabetical)

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1. List of Abbreviations

ACE: angiotensin converting enzime
CAG: coronary angiography
CTCA: computed tomography coronary angiography
CVD: cardiovascular disease
cMRI: cardiac magnetic resonance imagin
C-19CCC: COVID-19 Critical Care Consortium
ECMO: extracorporeal membrane oxygenation
EF: ejection fraction
GLS: global longitudinal strain
HLH: haemophagocytic lymphohistiocytosis
ICU: intensive care unit
MCS : mechanical circulatory support
PCI: percutaneous coronary intervention
POCUS: point of care ultrasound
ROSC: return of spontaneous circulation
RV: right ventricle
SARS-CoV2/COVID-19: Severe acute respiratory syndrome coronavirus-19

2. Introduction and Background

Acute cardiac injury is increasingly recognized following infection with SARS-CoV2 (a.k.a. COVID-19) and cardiovascular disease (CVD) risk factors are associated with both higher susceptibility to COVID-19 infection[1], and more severe disease course[2, 3]. Myocardial injury may manifest in a number of ways. In a recent report of 138 consecutive confirmed COVID-19 patients admitted to Zhongnan Hospital in Wuhan (January 1 to January 28, 2020) revealed that 16.7% experienced arrhythmias and a further 8.7% and 7.2% developed shock, and acute cardiac injury respectively (the latter defined as Troponin I >99th percentile ± new ECG or echocardiographic abnormalities)[1] and even biomarker evidence of injury portends significantly worsened outcomes in patients without known cardiovascular comorbidities; In patients without CVD comorbidity, raised TnT more than quadrupled hospital mortality in one series from 7.62% to 37.5%[4]. The mechanisms for myocardial injury remain to be elucidated, but may include direct invasion of the myocardium through ubiquitously expressed ACE2 receptors[5], haemophagocytic lymphohistiocytosis (HLH) overlap syndrome[6], or lymphocytic invasion and myocardial inflammation[7]. Additionally, neurogenic inflammation involving substance P pathways may mediate viral cardiomyopathy[8], cytokinaemia[9], and immune cell chemotaxis. The neurotropic potential of SARS-CoV2 [10,11,12], suggests putative central mechanisms may underly the sudden, cardiovascular collapse occurring in some patients[13]. Additionally, pulmonary thromboembolism may complicate COVID-19 associated respiratory failure, and potentiate acute right ventricular dysfunction[14].

Since the onset of reported cases of COVID-19 infection, there has been interest in the prognostic role of biomarkers, either in identifying a predominantly inflammatory phenotype of the disease, or to identify individuals at high risk of discrete complications such as myocardial infarction, and/or rapid deterioration. Multiple putative markers have been suggested, including C-reactive protein, lymphocyte count, interleukin-6 and lactate dehydrogenase. In particular, raised cardiac troponin and brain natriuretic peptide have been suggested as being most likely to be of prognostic value. Due to the heterogeneity of presentation and the lack of specificity of many biomarkers it is unlikely that a single biomarker will have sufficient predictive or prognostic value. A combination of key measures, however, may be able to be used. In addition to myocardial complications, vascular complications including disordered coagulation are frequent in severe COVID-19 infections. It may be that this dysregulation contributes to cardiac morbidity, hence combining interpretation of abnormalities in vascular biomarkers such as D-dimer, ferritin and platelets with cardiac biomarkers may be of value, of note, D-dimers recorded in a recent COVID-19 ARDS cohort were orders of magnitude greater than those seen in a contemporary cohort of non-COVID-19 ARDS patients[15]. Similar to HLH, a combination of clinical and biochemical parameters may be able to be used to predict the emergence of a pro-inflammatory phenotype of COVID-19 infection to ideally allow timely and appropriate intervention to limit subsequent cardiovascular collapse.

The aim of this observational, multicentric international study is to define the prevalence and nature of cardiac complications in critically ill, confirmed COVID-19 patients and, in doing so, assess the associated risk factors, predictors, and outcomes, and optimal management.

3. Study Objectives

3.1 Primary Aim

To report and characterize the incidence, risk factor, predictors, and outcome of acute cardiac complications in patients with COVID-19 who require admission to the intensive care unit, mechanical ventilation and/or pharmacological ± mechanical circulatory support. Further, to describe longer term morphologic and functional sequalae of this cohort of patients.

3.2 Secondary Aims

2.2a: Can deterioration of cardiac function in COVID-19 infection be predicted by monitoring changes in biomarker elevations?

2.2b: Is there a pro-inflammatory phenotype associated with myocardial injury in COVID-19 patients?

4. Study design

This is a sub-study of the observational international multicenter COVID-19 Critical Care Consortium (C-19CCC) observational study. As such, it will both prospectively and retrospectively recruit patients with COVID-19 requiring ICU admission at participating sites.

5. Methods

5.1 Sample Size

All patients with COVID-19 who meet the inclusion/exclusion criteria at participating sites will be eligible. Participating sites will be sourced from those within the C-19CCC who volunteer for this sub-study (see table).

Inclusion Criteria	1. Laboratory-confirmed COVID-19 2. Admission to an intensive care unit or other designated critical care area
Exclusion Criteria	1. Patients treated for other concomitant causes (other than COVID-19)

5.2 Primary and secondary outcomes

5.2.1 Primary Outcomes:

To identify the type, incidence and natural history of cardiac complications*in COVID-19 patients admitted to ICU.

*Cardiac complications
Myocardial infarction
Myocarditis
Takotsubo cardiomyopathy
Cardiac arrhythmias
Cardiogenic Shock
Cardiac arrest

5.2.2 Secondary outcomes

1. Mortality or case fatality due to cardiac complications

2. Duration of ICU and hospital stay in patients with cardiac complications

3. Risk factors and predictors for acute cardiac complications
   a. Demographics and prior cardiovascular morbidity
   b. Evolution and degree of abnormalities of a panel of readily available laboratory measures of inflammation, including C-reactive protein, Troponin, NT-proBNP, D-dimer, procalcitonin, ESR, ferritin, white blood cell count and platelet count.

4. Evolution of echocardiographic, biomarker, and electrocardiographic measures in critically ill patients with COVID-19

5. Cardiac complications associated with antiviral therapy

6. Cardiac complications resulting in the need for mechanical circulatory support, including but not limited to veno-arterial extra corporeal membrane support oxygenation (ECMO) support, Impella® devices, and intra-aortic balloon pumps. Data

related to outcomes and complications in patients treated with each therapies will also be collected

7. Imaging and adjunctive diagnostics:
   a. Echocardiograms: retrospectively reported by individual institutions, and prospective central reporting and post-processing. This will include transthoracic – full studies and POCUS abbreviated studies (point of care ultrasound), and trans-esophageal modalities +/- contrast enhancement.

   b. Coronary Angiography and coronary interventions performed

   c. Myocardial biopsy results
      i. Presence or absence of detectable SARS-CoV2
      ii. Characteristic inflammatory/cellular infiltrate

   d. ECG: Changes in PR,QRs, QTc intervals, morphology, rhythm and rate
      i. Dysrhythmias to be documented alongside interventions: pharmacological and electrical
      ii. Results of EP studies where performed: need for cardioversion, implantation of pacemaker device ±ICD

8. Recovering term follow up: Echocardiographic measure of biventricular function at discharge and functional status

5.3. Sub-Sub-studies

1. Echocardiography: centralized reporting of deidentified DICOM images
   a. GLS (global longitudinal strain) measurements and evolution in patients with acute cardiac injury
   b. Patterns of myocardial involvement : Could include microvascular contrast enhanced

2. Serum biomarker
   a. Myocardial injury marker Troponin and NT-proBNP
   b. Evolution of biomarkers of inflammation individually and in combination as available: CRP Ferritin, IL-6, procalcitonin, D-dimer, ESR, LDH, WCC and neutrophil/lymphocyte ratios
3. MCS sub-study: Characterizing types of MCS employed, impact of cannulation strategy cardiac indications for, and evolution of cardiac dysfunction on MCS.
4. Myocardial Biopsy (ante and post-mortem)

6. Recruitment

Potential patients will be identified and recruited in participating ICUs by the local investigators.

6.1 Eligibility

Inclusion Criteria

1. Laboratory-confirmed COVID-19 infection by real-time PCR and/or next-generation sequencing
2. Admission to an intensive care unit or other designated critical care area

Exclusion Criteria

1. Patients treated with mechanical ventilation for other concomitant causes (other than COVID-19)
2. Patients treated with ECMO for other concomitant causes

7. Methodology

Study population: All confirmed COVID-19 patients (≥18 y/o) admitted to ICU or similarly designated critical care areas and cardiology/coronary care units where dictated by local capacity.

Clinical and laboratory assessments: cf. Clinical Research Form (CRF)

At admission	1. Past medical History, Cardiac comorbidity 2. Past echocardiographic parameters (Within a year)
At discharge	The presence or absence of below 1. Acute myocardial infarction (CAG or CTCA, PCI or medication only) 2. Myocarditis (Echocardiography, cMRI, biopsy, biomarker) 3. Takotsubo cardiomyopathy (Echocardiography, cMRI) 4. Cardiac arrhythmia (medication only or pacemaker/cardioversion) 5. Cardiac arrest (location, time to ROSC, management) 6. Cardiogenic shock (management) 7. Other cardiac complications (e.g. Pericardial tamponade, Intracardiac thrombus) 8. Usage of MCS (e.g. ECMO/Impella®) 9. Echocardiographic parameters (geography, EF, GLS, valve dysfunction, RV function) 10. POCUS (size, wall thickness, function)

Data collection: Data collection method will follow the parent C-19CCC study, with a

dedicated cardiac subsection reporting form.

8. Statistical Methods

Continuous variables will be presented as median (interquartile range[IQR]), while categorical variables as number(percentage). The primary study analysis will be the calculation of the incidence rate of cardiological complications in COVID-19 patients. To this aim, incidence rate will be calculated as the number of events per ICU days. Actual confidence intervals of the incidence rate estimate will be calculated by means of the exact mid-p test for the secondary study analysis (assessment of predictors of 28-day case fatality), predefined, potential demographic and clinical predictors will be first tested for their association with the outcome in univariable logistic regression models. Then, factors potentially associated with 28-day case-fatality in univariable analysis ($p < 0.10$) will be included in an initial multivariable logistic regression model, and further selected for the final model by means of a stepwise backward selection procedure. Additional analyses (e.g., addition of a propensity score term to logistic regression models, use of penalized logistic regression techniques, or comparison of survival in subgroups through Kaplan-Meier curves) will be considered according to results of standard models, if deemed pertinent. The use of generalized linear mixed models based on logistic regression will also be considered for evaluating the impact on the outcome of center as a random effect. Covariates and outcome will be presented as nonlinear associations. For statistical significance a P value <0.05 will be considered. Analyses will be performed using SPSS statistical software (Version 26).

9. Administrative Aspects

Confidentiality: Study protocol, data collected, and other information will be strictly confidential. All data collected in eCRF will be anonymized and each center and each patient will receive an identification number, which is matched to the number used in the main study allowing cross referencing of data of interest.

Ethical considerations: The study will be conducted in compliance with the current version of the protocol. Protocol version and subsequent modifications will be approved by the local Ethic committees in compliance to national standards.

Financial disclosure and conflict of interests. All researchers are obliged to declare all their financial interests and conflict of interests.

10. Publications and Authorship policy

Ownership of the data arising from the study resides with the study teams. Data requested from SPRINT-SARI and EXCEL investigators will reside with their own study

teams. After the study, results will be analysed and tabulated, and a study report will be prepared. This report will be made available to the study collaborators and the relevant IRBs. The study findings will be presented at national and international meetings. We plan to publish our study findings in a high-quality peer reviewed journal. SPRINT-SARI and EXCEL studies will be fully acknowledged in all publications and presentations.

Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org). Authorship of parallel studies conducted outside of the main trial will be according to the individuals involved in the study but must acknowledge the contribution of the involved investigators.

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