CLINICAL STUDY PROTOCOL

Study Title:	**WHF COVID-19 and Cardiovascular Disease Survey**
Protocol Version:	**1.0**
Protocol Date:	**17 April 2020**
Sponsor:	**World Heart Federation, Geneva, Switzerland**
Collaborators:	**Public Health Foundation of India, India** **Centre for Chronic Disease Control, India** **University of Cape Town, South Africa** **London School of Hygiene and Tropical Medicine, UK**

CONTACT LIST

Principal Investigators

Prof. Karen Sliwa, MD, PhD, FESC, FACC, DTM & H
Director, Hatter Institute for Cardiovascular Research
University of Cape Town, South Africa
Email: karen.sliwa-hahnle@uct.ac.za

Prof. Dorairaj Prabhakaran, MD, DM (Cardiology), MSc, FRCP, FNASc.
Vice President, Research and Policy, Public Health Foundation of India
Executive Director, Centre for Chronic Disease Control (CCDC)
C-1/52, Second Floor, Safdarjung Development Area, New Delhi, India
Email: dprabhakaran@phfi.org

Prof. Pablo Perel, MD, MSc, PhD.
London School of Hygiene and Tropical Medicine
Keppel Street, London, WC1E 7HT, United Kingdom
Email: pablo.perel@worldheart.org

Co-Investigators

Prof. Fausto Pinto
President Elect, World Heart Federation
Dean of Faculty of Medicine, University of Lisbon, Portugal
Email: faustopinto@medicina.ulisboa.pt

Dr. Dike Ojji
University of Abuja Teaching Hospital, Abuja, Nigeria
Email: dike.ojji@uniabuja.edu.ng

Dr. Carolyn Lam
National Heart Centre Singapore, Singapore
Email: carolyn.lam@duke-nus.edu.sg

Dr. Friedrich Thienemann
University of Cape Town, South Africa
University Hospital Zurich, Switzerland
Email: friedrich.thienemann@usz.ch

Dr. Junbo Ge
Zhongshan Hospital, Chinese,
Chinese Cardiovascular Association, China
Email: ge.junbo@zs-hospital.sh.cn

Dr. Amitava Banerjee
University College London, UK
Email: ami.banerjee@ucl.ac.uk

Dr. Kristin Newby
Duke University Medical Center
Durham, North Carolina
Email: newby001@mc.duke.edu

Dr. Antonio Ribeiro
University Hospital at the Federal University of Minas Gerais
Brazil
Email: tom1963br@yahoo.com.br

Dr. Samuel Gidding
World Heart Federation
Email: samuel.gidding@gmail.com

Dr. Kavita Singh
Public Health Foundation of India
Email: kavita@ccdcindia.org

STUDY COORDINATION

Research Coordinating Centre (RCC) in India

Public Health Foundation of India (PHFI)
Plot. No. 47, Sector 44
Gurugram, Haryana-122002, India
AND
Centre for Chronic Disease Control (CCDC),
C-1/52, Second Floor,
Safdarjung Development Area,
New Delhi, Delhi-110016, India

RCC Team in New Delhi, India

Project Manager:

Research assistant:

Data manager: Mumtaj Ali

Biostatistician: Dr. Dimple Kondal

Table of Contents

1. Introduction 5

1.1 What is coronavirus? 5

1.2 Current COVID-19 pandemic 5

1.3 Link between Cardiovascular disease and COVID-19 6

1.3.1 Evidence from previous studies 6

1.3.2 Theories regarding pathophysiology 6

1.3.3 Emerging data from current pandemic 7

1.3.4. Rationale for the current study 8

2. Study Objectives 9

2.1 Primary objectives 9

3. Methods 9

3.1 Study design 9

3.2 Study setting 9

3.3 Study Population 9

3.4. Variables 10

3.5. Data collection 11

4. Data management 11

4.1 Source Data 11

4.2 Language 12

4.3 Database 12

4.4 Access to data, ownership, disclosure of data and publication 12

5. Sample size and analysis 13

6. Ethical issues 13

6.1 Institutional Ethics Committee Approval 13

6.2 Informed Consent 14

6.3 Participant's confidentiality 14

7. Study Management and governance 14

7.1 Study investigators 14

7.2 Study Steering committee 15

8. Study implications 15

9. References 16

1. Introduction

1.1 What is coronavirus?

Coronaviruses belong to a family of viruses that typically cause mild disease, such as the common cold, but also cause severe respiratory diseases such as Middle East Respiratory Syndrome (MERS-CoV) or Severe Acute Respiratory Syndrome (SARS-CoV) [1,2]. The novel coronavirus epidemic Coronavirus Disease 2019 (COVID-19) is caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), which invades cells by attachment to the angiotensin converting enzyme 2 (ACE2) receptor [1,2].

1.2 Current COVID-19 pandemic

COVID-19 is an emerging, rapidly evolving, global pandemic impacting nearly 210 countries and/or regions, and more than 1.9 million patients worldwide, with more than 125,000 deaths as of April 14, 2020 [2]. Available data indicate that COVID-19 is a relatively mild condition in most affected individuals but, in others, it can be very severe and deadly. Progression to pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure and death occurs, particularly in the elderly and those with key co-morbidities: chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), hypertension (HTN) and diabetes mellitus (DM). However, severe disease requiring hospitalization, and even deaths, have been reported in younger adults [2,3].

In December 2019, the novel *Coronavirus Disease 2019 (COVID-19)* outbreak started in Wuhan, the capital of Hubei province in China. Since then it has spread around the world. On 30 January 2020, the World Health Organization (WHO) declared the outbreak a “public health emergency of international concern”[2]. The spread onto the African continent and other low-income countries is of great concern. Large and densely populated areas and townships with widespread poverty and high migration are the most vulnerable populations for airborne pandemics. Existing epidemics of human immunodeficiency virus (HIV), tuberculosis (TB) and malaria are likely to collide with COVID-19 and may lead to morbidity and mortality patterns different from currently affected “hot spot” countries. Known risk factors for severe cases of COVID-19, COPD, CVD, HTN, and DM, have a high prevalence in low- and middle-income countries, and these conditions are generally worse controlled in these settings than

in high income countries and therefore the potential associated risk might be higher [3,4,5,6].

1.3 Link between Cardiovascular disease and COVID-19

1.3.1 Evidence from previous studies

CVD was a common comorbidity in patients with COVID-19 predecessors SARS and MERS [7,8,9]. In SARS, the prevalence of DM and CVD was 11% and 8% respectively, and the presence of either comorbidity increased the risk of death twelvefold. DM and HTN were prevalent in about 50% of cases of MERS, while CVD was present in approximately 30% of patients. The adverse impact on outcome of CVD comorbidities holds true for COVID-19 [8-12]. Analysis of an outpatient and inpatient cohort of 1,099 patients with COVID-19 reported that 24% had any comorbidity (58% among those with intubation or death), with 15% having HTN (36% among those with intubation or death), 7.4% with DM (27% among those with intubation or death), and 2.5% with coronary heart disease (9% among those with intubation or death) [13]. Data from the National Health Commission (NHC) of China showed that 35% of patients diagnosed with COVID-19 had HTN and 17% had coronary heart disease [14]. A meta-analysis of eight studies from China, including 46,248 infected patients, showed the most prevalent comorbidities were HTN (17±7%, 95% CI 14-22%), DM (8±6%, 95% CI 6-11%), and CVD (5±4%, 95% CI 4-7%) [15].

1.3.2 Theories regarding pathophysiology

The mechanism of the associations between COVID-19 and CVD are diverse [14,16]. The presence of compromised cardiac function or pulmonary hypertension will naturally limit a patient's ability to cope with respiratory or multi-organ failure. Older age is associated with higher prevalence of CVD, HTN, DM, and with a functionally impaired immune system. For example, 50% of adults older than 65 years of age who receive the influenza vaccine have low protective titers [10]. COVID-19 infection sets off an acute inflammatory storm, in fact, the robust inflammatory response is responsible for progressive lung injury. This response may also lead to myocardial injury

and impaired cardiac function [17,18]. COVID-19 infection is initiated by the binding of the virus with the ACE-2 receptor [19]. This has led to speculation concerning the predilection of COVID-19 for those with hypertension or CVD and consideration of whether or not medications that block ACE-2 are helpful or harmful to patients. By upregulating ACE-2, these medications may increase susceptibility; on the other hand ACE-2 is important as a host defense against lung injury from acute respiratory defense mechanism and the medications improve cardiac function [19]. Urgent research in this area is needed.

There is concern that COVID-19 is cardiotropic, based on the high prevalence of findings consistent with myocardial injury, disturbances of cardiac function, presence of pericardial effusions in some patients, and absence of obstructive coronary disease in patients with acute myocardial injury and suggestive ECG changes. Autopsy findings confirm, in some patients, the presence of myocarditis but characterization of the pathophysiology remains incomplete. One pathological investigation included biopsy samples at autopsy of a patient who died of COVID-19; these showed a few mononuclear inflammatory infiltrates in the myocardial interstitium, without substantial damage in the heart tissue.

1.3.3 Emerging data from current pandemic

COVID-19 interacts with the cardiovascular system on multiple levels. Individuals with underlying chronic CVD are both more susceptible to COVID-19 and more prone to myocardial injury and dysfunction, critical deterioration and death. Patients with COVID-19 and CVD had a much higher fatality rate (10.5%) with COVID-19 and HTN (6.0%), as compared to 0.9% in patients with no reported comorbid conditions. Arrythmias are present in 17% of patients.

Myocardial injury, evidenced by elevated cardiac biomarkers, was recognized among early COVID-19 cases in China [19,20,21]. In a study of 138 hospitalized patients with COVID-19 in Wuhan China, cardiac injury (elevated high sensitivity Troponin I [hs-cTnI] or new ECG or echocardiographic abnormalities) was present in 7.2% of patients, and 22% that required ICU care. In meta-analysis of all Chines reports, about 8-12% of patients had elevated troponin levels, or cardiac arrest during the hospitalization [22].

Notably, hs-cTnI was above the 99th percentile upper reference limit in 46% of non-survivors as opposed to 1% of survivors. Patients with myocardial injury also had evidence of more severe systemic inflammation, including greater leukocyte counts and higher levels of C-reactive protein and procalcitonin as well as high levels of other biomarkers of myocardial injury and stress, such as elevated creatine kinase, myoglobin, and NT-proBNP. This injury has been attributed to multiple causes in individual patients: myocarditis, acute myocardial inflammation, or acute myocardial infarction. Patients who developed myocardial injury with COVID-19 had clinical evidence of higher acuity, with a higher incidence of acute respiratory distress syndrome and more frequent need for assisted ventilation than those without myocardial injury.

Acute pulmonary infection may destabilize CVD, including heart failure and atherosclerosis, including precipitating acute myocardial infarction, which has been reported in the pandemic. Deterioration of cardiac function would then, in turn, exacerbate COVID-19 management [23,24].

1.3.4. Rationale for the current study

As summarized above although there is emerging evidence that CVD, DM, and HTN are associated with COVID19 and its severity. COVID-19 may be cardiotropic in a subset of patients. Both acute and pre-existing CVD impact outcomes unfavorably. It is possible that one common CVD treatment, medications that impact ACE-2 function, may impact outcomes either favorably or unfavorably.

However, studies so far have, perforce, been conducted with important limitations (e.g. small numbers, limited geographical representation, lack of data standardization for risk factors and outcomes, limited measurement, lack of appropriate adjustment for important confounders, and missing data) [25]. Considering the high global prevalence of CVD and its risk factors (e.g. hypertension and diabetes) and the suggested link with COVID19 it is urgent to initiate more robust studies to clarify the many issues early reports have engendered.

In order to reach robust conclusions that could inform clinical and policy practices, we will conduct a global study for a better understanding of the

cardiovascular conditions that increase the risk of developing severe COVID-19, and a better characterization of cardiovascular complications in hospitalized patients with COVID-19.

2. Study Objectives

2.1 Primary objectives

2.1.1 To describe *cardiovascular outcomes* among patients hospitalized with COVID-19;

2.1.1 To identify *cardiovascular risk factors* associated with poor in-hospital prognosis among patients with COVID-19;

3. Methods

3.1 Study design

We will conduct a prospective cohort study including consecutive confirmed COVID-19 patients.

3.2 Study setting

Participants will be recruited in any hospital where COVID19 patients are hospitalized. We will invite all WHF members from 100+ countries to identify at least two recruiting centres in their respective countries. Each centre should recruit between 50 and 200 consecutive patients. There is no limit in the number of sites to take part.

3.3 Study Population

3.3.1 Eligibility criteria

3.3.1.1 *Inclusion Criteria*

- All adult (as locally defined) with confirmed COVID-19 infection who are hospitalized are eligible.

3.3.1.2 Exclusion criteria

- Patients for whom we are unable to obtain informed consent will be excluded.
- Patients who are unlikely to stay in the recruiting centre for 30 days (i.e. likely to be transferred)

3.3.2 Follow up

All patients will be followed up until 30 days, death or discharge whichever occurs first. If patient is discharged prior to 30 days, a phone contact will be made to find out whether patient is alive or dead or if the patient had any re-hospitalization.

3.4. Variables

We will collect the following data variables.

Centre level: each center will provide the following information only once at the beginning of the study: Estimated size of population served, total number of beds, number of ICU beds, number of ventilators, number of cardiologists, availability of echocardiogram (including point-of-care ultrasound), number of primary PCI cases/ ECMO/ heart transplantations performed per year prior to the COVID-19 outbreak

Patient level

3.4.1. Exposures

- *Patient demographics:* age, sex, ethnicity, weight/height and education level,
- *Clinical history:* smoking status, hypertension, diabetes, obesity, heart failure, rheumatic heart disease, chagas, history of Coronary artery disease/ Percutaneous Coronary Interventions/ Coronary artery bypass graft surgery
- *Usual medication (before hospitalization)*
- *Clinical characteristics at presentation:* confirmed diagnosis of COVID-19, heart rate, blood pressure,
- Tests: ECG, ECHO, troponin, NT-proBNP and other biochemical markers
- Medication received during hospitalization: cardiovascular and non-cardiovascular medications.

3.4.2. Outcomes

- Need of intensive care, need of ventilator,
- death (with cause),
- major adverse cardiovascular events (myocarditis, arrhythmia, heart failure [including Left ventricular ejection fraction], acute coronary event [type of Myocardial infarction]),
- neurological outcomes,
- pulmonary outcomes

3.5. Data collection

This study will be coordinated from PHFI and CCDC (India) and conducted in hospitals in low-, middle- and high-income countries. Data will be collected at each site by local investigators and sent to the coordinating center. Only data outlined on the entry and outcome forms will be collected. Each site will have a research coordinator who will enter in-hospital entry and outcome form via a secure website throughout the entire study period. Hospital-level data will be collected just once when the hospital joins the study.

We will use an electronic form (redcap) to collect entry and outcome forms. The entry form will be used at hospital admission to collect baseline data. The outcome form will be completed 30 days after hospital admission or death or hospital discharge whichever occurs first. These data will be collected from the patient's routine medical records and no special tests will be required. We will also collect data on ECG (scanned copies of ECG and/or digital files) and echocardiogram (raw DICOM) conducted as part of the usual clinical care of patients. ECG exams will be uploaded to a web-based platform to be read and codified, according to the Minnesota Code, by experienced and certified cardiologists. Automatic measurements of ECG intervals, including the QT interval, will be reviewed. ECG (xml or image files) and echo images (raw DICOM) will be anonymized at sites via provided software and sent via encrypted cloud for central reading [26,27].

4. Data management

4.1 Source Data

Data will be collected directly from the patient's routine medical records, clinical notes at hospital admission, and at 30 days, discharge or death, whichever occurs first, using CRFs administered by study investigators. If a patient is discharged before 30 days investigators will make a phone contact to find out whether patient is alive or death at 30 days and if the patient had re-hospitalization.

The CRF (source notes) will be completed in English for each enrolled patient. Study personnel and the principal investigator at each centre will be responsible for evaluating the CRFs for accuracy and completeness before entering into the online electronic clinical data management system. Once entered, the data manager will review the data for discrepancies and missing data. The site will then be informed to

make any required corrections and/or additions and the CRF's stored until all analyses are completed. The principal investigators and the study site research coordinator will be required to respond to the data queries and confirm and correct the data. A printed copy of the CRF and individual informed consents will be maintained in the participant's file. Confidentiality of participant's data will be maintained in accordance with national laws with the informed consent form containing a statement describing the extent to which confidentiality of the participant will be maintained.

4.2 Language

CRFs will be in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by participants will use vocabulary that is clearly understood and be in the language appropriate for the study site.

4.3 Database

Study personnel at the participating sites will be responsible for completing CRFs through remotely accessing a centralized electronic clinical data management system. Appropriate training will be provided to the clinic site teams for entering data into the electronic data capture system by the project manager. CCDC will be serving as the Research Coordinating Centre and will have access to all the study data. Individual sites will have access to their own centers' data and will be provided site-specific data summaries by CCDC's data management team, upon request.

4.4 Access to data, ownership, disclosure of data and publication

The Sponsor and coordinating center (PHFI/CCDC) are responsible for storage, protection and retrieval of registry data. The Steering Committee is responsible for the guardianship and use of the data. PHFI/CCDC will have access to all the study data. Individual sites will have access to their own centers' data. Each site personnel who is responsible for entering and reviewing participant data on the Electronic Clinical Data Management System will be provided access with a secure password. Sites will be provided with site-specific data summaries by CCDC, upon request. All vetted researchers will be given free access to the online platform and machine learning tools to do further research.

All publications will be approved by the Steering Committee who will be named on all reports. The research teams, research nurses, collaborating doctors, and their respective units will be named, and study participants acknowledged in the final report and in publications arising from this registry. Acknowledgement in a future publication will be offered to all participating centers, national leaders, and site investigators that have provided valid data sets according to the publication rules of the European Society of Cardiology (ESC) and EURObservational Research Programme (EORP). The ESC is a member of the World Heart Federation.

5. Sample size and analysis

We will invite all WHF members (Scientific Societies and Foundations) from 100+ countries to take part in this study. Assuming that 35 members identified at least 2 hospital sites, recruiting an average of 75 patients each, we will be able to recruit 5,200 participants. Assuming an incidence of 8% of an adverse outcome such as myocarditis we will have more than 90% power to detect this adverse outcome with 95% confidence and a margin of error of 2% (confidence interval).

Further, with this sample size of >5000 COVID-19 patients, and assuming a proportion of potential cardiovascular risk factor (hypertension)as 20% we will have more than 80% power to detect a relative risk of 2.0 for poor outcomes (death, myocarditis, and other major adverse cardiovascular events). Interim analyses will be conducted to test our initial assumptions and if necessary we will extend our recruitment and increase our sample size accordingly.

Statistical analyses: Data will be reported as a number (proportion) of patients for categorical variables, mean (SD) for normally distributed continuous variables, and median (IQR) for skewed distributions. Data-derived and previously published multivariate models for in-hospital or post-discharge mortality and complications will be used to adjust for significant covariates.

6. Ethical issues

6.1 Institutional Ethics Committee Approval

All investigators will obtain ethical approval from their institutional ethics committees. Eligible patients will be approached regarding potential participation in the study and the study purpose, risks, and potential benefits will be explained by the study

coordinator and/or principal investigators. Potential patients will be given the opportunity to ask questions. Patients who voluntarily agree to participate in the study will be asked to document their informed consent.

6.2 Informed Consent

The investigator or the person designated by the investigator should fully inform the patient of all the important aspects of this observational study, including the approval by the ethics committee of the study protocol. Prior to the participation of the patient in the study, the informed consent form should be signed and personally dated by either the patient or the patient's legally acceptable representative, and by the person who conducted the informed consent interview. For those patients who are directly unable to provide written informed consent (due to admitted in ICU or unconscious), consent could be obtained from a legally acceptable representative and/or in the presence of an impartial witness if acceptable by local regulation.

6.3 Participant's confidentiality

Study data sent to the Electronic Data Management System at the Research Coordinating Centre at CCDC will be securely stored. Source documents pertaining to the study which is maintained in each participating site will be stored securely by the site coordinator, in accordance with the ethical requirements. Informed consent will be obtained from the participants to collect, transmit and store identifiable personal information. Identifiable data collected during this study will be replaced by a code number.

7. Study Management and governance

7.1 Study investigators

Principal Investigators

Karen Sliwa, Dorairaj Prabhakaran, Pablo Perel

Co-investigators

Fausto Pinto, Dike Ojjii, Carolyn Lam, Friedrich Thienemann, Junbo Ge, Amitava Banerjee, Kristin Newby, Antonio Ribeiro, Samuel Gidding and Kavita Singh.

National Leaders and site investigators will constitute the larger team contributing to this registry and will be acknowledged to future publications as per the ESC and EOPR publications and authorship policy.

7.2 Study Steering committee

The **Steering Committee** will be the decision-making body of this registry. It will consist of members of PHFI and CCDC, India (Drs. Dorairaj Prabhakaran and Kavita Singh), LSHTM, UK (Dr. Pablo Perel) and University of Cape Town, South Africa (Prof. Karen Sliwa) will meet, via telephone conference, on approximately a weekly basis (or less frequently if deemed appropriate) to address the operational and scientific matters of the study. The Steering Committee will make the major decisions regarding the project, including:

· the scientific direction of the project, including partner responsibilities and any changes in budgetary allocations,

· the dissemination and exploitation strategy; and

· any administrative and legal decisions relating to the registry's contractual obligations to the study sponsor (World Heart Federation).

The daily administrative, scientific and technical management of the project will be executed by a **Project Management Team** based at PHFI/CCDC and LSHTM, consisting of the Principal Investigator (Prof. Dorairaj Prabhakaran), Co-PI (prof. Pablo Perel), co-investigator (Dr. Kavita Singh) and the Project Manager. The Project Management Team will help carry out the decisions of the Steering Committee and will be supported in its tasks by the administrative resources based at PHFI/CCDC.

8. Study implications

This global cohort study will provide insights into the cardiovascular outcomes and cardiovascular risk factors among hospitalized patients with confirmed COVID19. By providing comparable data from countries around the globe, the study will inform the delivery of care for patients with COVID19, with underlying cardiovascular conditions or with cardiovascular complications.

9. References

1. Thienemann F, Pinto F, Grobbee DE, Boehm M, Bazargani N, Ge J, et al. World Heart Federation Briefing on Prevention: Coronavirus Disease 2019 (COVID-19) in low-income countries. *Global Heart*. 2020; 15(1): 23. DOI: https://doi.org/10.5334/gh.778
2. WHO. Coronavirus disease 2019 (COVID-19) situation report—56. March 16, 2020.https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200316-sitrep-56-covid-19. pdf?sfvrsn=9fda7db2_6.
3. Wu Z, McGoogan J M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. Published online February 24, 2020. DOI:10.1001/jama.2020. 2648
4. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol*. 2020.
5. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet*. 2020. https://www.thelancet.com/ journals/lancet/article/PIIS0140-6736(20)30566-3/fulltext.
6. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020. (March 11, 2020).
7. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med*. 2004; 351(25): 2611–8. DOI: https://doi.org/10.1056/NEJMoa041747
8. Alsahafi AJ, Cheng AC. The epidemiology of Middle East respiratory syndrome coronavirus in the Kingdom of Saudi Arabia, 2012–2015. *Int J Infect Dis*. 2016; 45: 1–4. DOI: https://doi.org/10.1016/j. ijid.2016.02.004
9. Alhogbani T. Acute myocarditis associated with novel Middle East respiratory syndrome coronavirus. *Ann. Saudi Med*. 2016; 36: 78–80. DOI: https://doi.org/10.5144/0256-4947.2016.78
10. Nguyen JL, YangW, Ito K, Matte TD, Shaman J, Kinney PL. Seasonal influenza infections and cardiovascular disease mortality. JAMA Cardiol. 2016;1(3):274-281.
11. Madjid M,Miller CC, Zarubaev VV,et al. Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34,892 subjects. Eur Heart J. 2007;28(10):1205-1210. DOI: 10.1093/eurheartj/ehm035
12. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5
13. Guan W J, Ni Z Y, Hu Y, et al. China Medical Treatment Expert Group for COVID-19. Clinical characteristics of coronavirus disease in 2019 in China. N Engl J Med. Published online February 28, 2020.

14. Zheng Y-Y, Ma Y-T, Zhang J-Y and Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. March 5, 2020. doi: 10.1038/s41569-020-0360-5. [epub ahead of print].
15. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y and Zhou Y. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis. March 12, 2020. doi: 10.1016/j.ijid.2020.03.017. [epub ahead of print].
16. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA Cardiol. Published online March 27, 2020. DOI:10.1001/ jamacardio.2020.1286
17. Kwong J C, Schwartz K L, Campitelli M A, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med. 2018;378(4):345-353.
18. Hui H, Zhang Y, Yang X, Wang X, He B, Li L, Li H, Tian J, Chen Y. Clinical and radiographic features of cardiac injury in patients with 2019 novel coronavirus pneumonia. *Medix*. 2020. DOI: https://doi. org/10.1101/2020.02.24.20027052
19. Oudit G Y, Kassiri Z, Jiang C, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest. 2009;39(7):618-625. DOI:10.1111/j. 1365-2362.2009.02153.x
20. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. Published online March 25, 2020. DOI:10.1001/ jamacardio.2020.0950
21. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. Published online March 27, 2020. DOI:10.1001/ jamacardio.2020.1017
22. Lippi G, Lavie CJ, Sanchis-Gomarc F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis. Prog Cardiovasc Dis. 2020 Mar 10. doi: 10.1016/j.pcad.2020.03.001 [Epub ahead of print].
23. Yang C, Jin Z. An acute respiratory infection runs into the most common noncommunicable epidemic—COVID-19 and cardiovascular diseases. JAMA Cardiol. Published online March 25, 2020. DOI:10.1001/jamacardio.2020.09.
24. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol. Published online March 27, 2020. DOI:10.1001/jamacardio.2020.1096
25. WHO. Global research on coronavirus disease (COVID-19). *Database of publications on coronavirus disease (COVID-19)*. https://www.who.int/emergencies/ diseases/novel-coronavirus- 2019/global-research-on-novel- coronavirus-2019-ncov
26. Ribeiro AH, Ribeiro MH, Paixão GMM, et.al. Automatic diagnosis of the 12-lead ECG using a deep neural network. Nat Commun. 2020 Apr 9;11(1):1760.
27. Alkmim MB, Silva CBG, Figueira RM, et.al. Brazilian National Service of Telediagnosis in Electrocardiography. Stud Health Technol Inform. 2019 Aug 21;264:1635-1636.