



ISARIC (International Severe Acute Respiratory and Emerging Infections Consortium)

A global federation of clinical research networks, providing a proficient, coordinated, and agile research response to outbreak-prone infectious disease

Analysis Plan for ISARIC International COVID-19 Patients

Title of proposed research
Cardiovascular comorbidities and complications in hospitalized patients with COVID-19
Version: (Date: Day/Month/Year)
22/3/2022
Working Group Chair (name, ORCID ID, email, institution, country)
Christiana Kartsonaki (christiana.kartsonaki@dph.ox.ac.uk , University of Oxford, ORCID: 0000-0002-3981-3418)
¹ Working group co-chair (name, ORCID ID, email, institution, country)
Lydia Harrison (lydia.harrison@new.ox.ac.uk , New College, University of Oxford) Asri Ranga Bin Abdullah Ramaiah, sriranga71@hotmail.com , Serdang Hospital, Malaysia Sheamini A/P Sivasampu, sheamini@crc.gov.my , Centre for Clinical Outcome Research, Malaysia, ORCID: 0000 0003 2314 6048
Statistician (name, ORCID ID, email, institution, country)
Lydia Harrison (New College, University of Oxford) Christiana Kartsonaki (University of Oxford)

¹ Either chair and/or co-chair are based in an institution in an LMIC. If you would like to be connected with an eligible co-chair please let us know at ncov@isaric.org.

Final draft SAPs will be circulated to all ISARIC partners for their input with an invitation to participate. ISARIC can help to set up collaborator meetings; form a working group; support communications; and accessing data. Please note that the details of all approved applications will be made publicly available on the ISARIC website. Please complete all sections of this form fully and return to ncov@isaric.org

Introduction

Individuals with pre-existing cardiovascular disease have higher risks of adverse outcomes if infected with SARS-CoV-2. Additionally, studies have shown that COVID-19 is associated with cardiovascular complications, including long-term complications even among individuals with initially non-severe COVID-19. It is therefore of interest to better understand the relationship of pre-existing cardiovascular disease with COVID-19 presentation and outcomes among individuals infected with SARS-CoV-2, as well as the risks of short-term cardiovascular complications among hospitalized patients with COVID-19, including those with and without cardiovascular comorbidities. The aims of this project will be to investigate the presentation and outcomes in individuals with and without cardiovascular comorbidities, as well as to explore cardiovascular complications of COVID -19.

The project will consist of a literature review and analysis of data from ISARIC on hospitalised patients with COVID -19. A Medical Sciences Final Honour School (FHS) student project at the University of Oxford will be based on the work included in this SAP.

This document details the initial analysis plan for publication on a subset of COVID-19 patients in the global cohort in the ISARIC database, as of January 2022. There are currently 52 countries contributing data and these have so far contributed data on ~800,000 patients. These data will represent the global experience of the first 2 years of this pandemic.

Participatory Approach

This is the standard ISARIC collaborative analysis approach. Please amend if you would like to suggest any changes.

All contributors to the ISARIC database are invited to participate in this analysis through review and input on the statistical analysis plan and resulting publication. The outputs of this work will be disseminated as widely as possible to inform patient care and public health policy, this will include submission for publication in an international, peer-reviewed journal. ISARIC aims to include the names of all those who contribute data as cited collaborators of this publication, subject to the submission of contact details and confirmation of acceptance of the final manuscript within the required timelines, per ICMJE policies and the ISARIC publication policy.

Research Plan

Summary of Research Objectives
Cardiovascular comorbidities and complications in hospitalized patients with COVID-19
Proposed Target Population
Hospitalised patients with COVID-19
Clinical Questions/Descriptive Analyses
<p>What are the risks of adverse outcomes (death, admission to ICU, use of IMV) associated with cardiovascular comorbidities (e.g. pulmonary embolism/DVT/VTE, myocardial infarction, heart failure, stroke)?</p> <p>What are the risks of cardiovascular complications (pulmonary embolism/DVT/VTE, myocardial infarction, heart failure, stroke and others)?</p>
Planned Statistical Analyses, Methodology and Representation
<ul style="list-style-type: none"> • Calculate frequencies of the types of (a) cardiovascular comorbidities and (b) cardiovascular complications, overall and by country • Describe the demographic and clinical characteristics of patients with cardiovascular disease (CVD) in ISARIC including age, sex, country, other comorbidities, smoking, and BMI • Describe the clinical features and severity of COVID-19 in patients with different cardiovascular comorbidities (pulmonary embolism/DVT/VTE, myocardial infarction, heart failure, stroke and others) • Investigate the reasons for admission, where data are available • Compare the symptoms at presentation between patients with CVD and all others • Describe the clinical and laboratory variables that are associated with COVID-19 severity and mortality among patients with CVD • Treatments used in patients with CVD vs others • Determine the COVID-19 fatality rate in patients with CVD vs others • To determine the association of CVD with risk of death and complications • To describe the use of healthcare resources (including intensive care and IMV) in the treatment of COVID-19 in patients with CVD vs others • To describe the risk of cardiovascular complications in the entire cohort and by pre-existing CVD status (estimate transition probabilities between the different states: prior CVD [no, specific major types], new CVD [no, specific major types]). <p>Methods:</p>

1. Overall frequencies of key demographic variables.
2. Frequencies of reasons for admission (or onset of COVID-19 symptoms before/after hospitalisation).
3. Frequencies of symptoms at presentation of patients with and without CVD.
4. Frequencies of comorbidities and risk factors among patients with and without CVD.
5. Medians and IQRs of serology measurements among patients with and without CVD.
6. Frequencies of treatments administered to patients with and without CVD.
7. Cox proportional hazards models will be fitted to estimate hazard ratios of death, ICU admission, and use of IMV comparing patients with and without CVD. Potential confounders will be identified and adjusted for. The proportional hazards assumption will be assessed using Schoenfeld residuals.
8. Outcomes of patients with CVD by age, sex and over time.
9. Risk of cardiovascular complications overall and by CVD status.

Analyses will be done overall and where data are available by type of CVD.

Subgroup analyses will be done by age, sex, region, time period, any proxy of performance status.

Handling of Missing Data

Analysis will be performed to ascertain a detailed overview of the extent of missingness in the data. This should enable the identification of variables which lack sufficient data to allow for any useful analysis to be performed on them. The type of missingness will be considered including whether data are not missing at random and follow-up with sites will be conducted if appropriate. If appropriate, imputation will be performed using Multiple Imputation by Chained Equations (MICE).

Other Information

Findings will be written up as a FHS project and will be submitted for publication.

References

Xie, Y., Xu, E., Bowe, B. *et al.* Long-term cardiovascular outcomes of COVID-19. *Nat Med* (2022). <https://doi.org/10.1038/s41591-022-01689-3>

ISARIC Clinical Characterisation Group, Christiana Kartsonaki. Characteristics and outcomes of an international cohort of 400,000 hospitalised patients with Covid-19. medRxiv 2021.09.11.21263419; doi: <https://doi.org/10.1101/2021.09.11.21263419>