



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

Please complete the following sections:

Title of proposed research
Neurological manifestation and outcome for patients admitted to hospital with COVID-19: Results from the ISARIC prospective multinational observational study
Version: (Date: Day/Month/Year)
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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

In late December 2019, a novel coronavirus was identified in Wuhan, China[1]. The rise in daily confirmed cases lead the World Health Organization (WHO) to declare severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection as a global pandemic[2–7]. The typical initial manifestations of COVID-19 combine fever (98%), cough (76%), lymphopenia (63%), leukopenia (25%), myalgia and asthenia (18%). Upper airway involvement is rare[8]. Hospitalization is frequently required in those patients who are infected and present severe respiratory distress (67%). Intensive care unit (ICU) admission is reserved to most severe patients who require critical care management (27%), of whom up to 25% develop life threatening conditions[9]. Recent findings suggested that COVID-19 patients may also develop neurological and neuropsychiatric symptoms by a mechanism(s) not yet elucidated[10]. The systemic inflammatory process, the hypercoagulability state, and the viral neurotropism are a few of the possible mechanisms involved. To date, neurological and neuropsychiatric manifestations (hereafter referred to as neurological manifestations) have been characterized into three main areas: central nervous system disorders, peripheral nervous system disorder and skeletal muscle symptoms[10].

It is well known that neurological outcome in critically ill patients can be influenced by the development of secondary brain damage, and that COVID-19 patients frequently present hypoxia, as a result of severe respiratory distress, hypotension, and microvascular abnormalities. Thus, it can be hypothesized that one of the possible mechanisms involved in neurological manifestations of COVID-19 patients could be the promotion of neuroinflammation and excitotoxicity with increased permeability of the blood brain barrier[11]. Secondary brain injuries can also be related to systemic disturbances (e.g. hypoxemia, hypocapnia, fever, anemia, hyponatremia) which may exacerbate the primary cerebral damage resulting from secondary brain injury[12]. The aim of this observational multicentric international study is to identify the prevalence of neurological manifestations in critically ill confirmed COVID-19 patients and to assess risk factors and outcomes of neurological complications of COVID-19. This document provides the details of the initial analyses planned for publication on a subset of COVID-19 patients in the global cohort in the ISARIC database, as of 20 Aug 2020. There are currently 42 countries (as of 17 September 2020) contributing data and these have so far contributed data on 96074 patients. This data will represent the global experience of the first 7 months 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 in the cited authorship 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
This is a multi-centre international observational study in patients with COVID-19 to report and characterize the prevalence, risk factor, and outcome of neurological manifestations.
Proposed Target Population
We will include all patients with COVID-19 who require admission to the hospital, intensive care unit, mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO).
Clinical Questions/Descriptive Analyses
<p>1. What are the different types of neurological manifestations at admission and their prevalence?</p> <ul style="list-style-type: none">- <i>Anosmia</i>- <i>Ageusia</i>- <i>Seizure</i>- <i>Confusion</i>- <i>Altered Behaviour</i>- <i>Coma</i>

-Fatigue

-myalgia

-joint pain

-Anorexia

- Anxiety

- Depression

2. What are the different types of neurological complications and their prevalence?

-Stroke (ischaemic and haemorrhagic)

-Seizure

-Meningitis

3. Neurological complications (ccm_b_horeas + seizure_ceterm + stroke_ceterm + meningitis_ceterm)

- Age stratified analysis

- ccm_b_cfs_rsyn

- ccm_b_prism_rsorres

-Sex stratified analysis

-Race stratified analysis

-Comorbidities

-Lab values

4. Stroke and its risk factors

- Age

-Sex

-Race

-Comorbidities

-Lab values (including d-dimers, platelet count and fibrinogen)

Association with laboratory markers of inflammation: IL-6, WBC/Lymphocyte ratio, C-Reactive protein, Ferritin, D-Dimer, Anticardiolipin & Antiphospholipid antibodies

Admission NIHSS score in centers who capture this

-Non-hospitalized vs. hospitalized vs. ICU vs. ECMO (Is ECMO a risk factor of stroke?)

5. What's the outcome of neurological complications?

-Mortality (compare with non-neurological complication patients) of each type of neurological complication

- EQ5D scale analysis if available

6. Interventions for neurological complications

- *Thrombolytics, anticoagulants*
- *Endovascular retrieval of proximal arterial thrombus*
- *Therapeutic plasma exchange*
- *Corticosteroids*
- *IV-Immunoglobulin*

7. Exploratory

– bleeding complication (text: CNS, brain, cerebral hemorrhage) risk factors

Planned Statistical Analyses, Methodology and Representation

1. Overall frequencies of key neurological manifestation (admission and follow-up) /diagnosis variables (primary) and frequencies stratified by sex/gender, race, and adult vs. pediatric (<18 year-old) (secondary).
2. Overall frequency of all neurological complications combined
3. Comparison of prevalence in non-ICU vs. ICU patients
4. Comparison of prevalence in ECMO vs. non-ECMO patients
5. Bar plots for displaying frequencies of each neurological diagnosis
6. Proportions will be presented by 10-year age band, sex, and race/ethnicity
7. Continuous variables will be presented as median (interquartile range [IQR]) and means with 95% confidence intervals, while categorical variables as number (percentage).
8. Prevalence will be calculated by dividing the number of patient's cases with at least one neurological manifestation (admission and follow-up) by the total number of patients with SARS-CoV-2 infection included in the hospital. Overall prevalence by neurological manifestation will be summarized by a mean and 95% confidence interval. Associations between prevalence and risk factors will be examined using penalised logistic regression (LASSO). Proportional logistic regression models for continuous non-normally distributed variables with defined covariates will be used.

9. Cox hazards regression analysis will be used for 28-day mortality or discharge mortality as the primary endpoint. Results will be visually presented as Kaplan Meier curve, for i) all neurological complications, ii) Stroke, iii) Seizures, and iv) meningitis. Covariates and outcome will be presented as nonlinear associations. We will perform a multi-state analysis to estimate the mean LOS, mean duration of MV/ECMO and risk of death and discharge.
10. Correlation coefficients demonstrating the association between markers of inflammation (IL-6, WBC/Lymphocyte ratio, C-Reactive protein, D-Dimer) and the development of stroke, peripheral neuropathy, delirium, meningitis/encephalitis
11. Was the risk of neurologic symptoms altered by the exposure vs non-exposure to antiviral therapies?

Handling of Missing Data

Preliminary analysis would 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. Type of missingness shall be considered including whether data are not missing at random and follow-up with sites will be conducted if appropriate. Variables with greater than 30% missingness will be excluded from analysis. Where appropriate, imputation will be performed using Multiple Imputation by Chained Equations (MICE).

Other Information

Provide details of the timelines for dissemination of research findings.

- ☐ As soon as our proposal is accepted, we will submit the manuscript within a month.

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