ISARIC

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
Monitoring of COVID-19-associated outcomes across countries and over time in relation to the publication of therapeutic guidelines
Version: (Date: Day/Month/Year)
8 December 2021
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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

Write a brief summary introduction of the population, problem and analysis you would like to undertake. You may follow the example used in the stock text below.

This document details the initial analysis plan for publication on all COVID-19 patients in the global cohort in the ISARIC database, as of 8 December 2021. This analysis addresses time trends in outcomes across countries and over time in relation to the publication of therapeutic guidelines for COVID-19.

BACKGROUND:

- Life-saving therapies recommended the world over include immunosuppressive medications.
- In most clinical trials, the survival benefit was ascertained after a short follow-up period and participants from low-middle income countries were underrepresented.
- Globally, various groups are expressing concern that the survival benefit associated with immunosuppressive medications may be reduced or even disappear over time as the risk of dying from opportunistic infections increases, particularly in low-middle income countries where the prevalence of mycobacterial and fungal pathogens is greater.
- Post-dissemination monitoring of guideline implementation and impact is crucial (see Trustworthy guidelines).
- This analysis of the risk of death and, where available, opportunistic infections and guideline uptake, over time and across WHO regions, will either provide reassurance or raise additional concerns regarding the possibility that certain risks posed by recommended interventions may have been under-measured in the clinical trials that informed guidelines.

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

1) To report mortality by time epoch (weekly/monthly) globally and by WHO region, in relation to the publication of therapeutic guidelines for COVID-19
2) To analyze and compare across countries/WHO regions mortality rates before and after the publication of therapeutic guidelines for COVID-19, in relation to treatments availability and wealth levels.
3) To assess how mortality-over-time trajectories vary according to wealth level and opportunistic infections prevalence in sites/regions, in relation to the publication of therapeutic guidelines regarding immunosuppressive medications.
4) (If available) To assess rates of opportunistic infections in patients hospitalized with COVID-19, overall and in relation to the publication of therapeutic guidelines.
5) (If available) To describe rates of treatment administrations by time epoch and severity level in relation to the publication of therapeutic guidelines for COVID-19.
6) (If available) To assess risk of opportunistic infection in patients hospitalized with COVID-19 based on administered treatment and opportunistic infections prevalence at site of hospitalization (adjusted for??).
7) To assess the risk of mortality in patients hospitalized with COVID-19 based on administered treatment

Proposed Target Population

- All patients in the global ISARIC cohort

Clinical Questions/Descriptive Analyses

<u>Analyzes based on site(hospital/countries/WHO regions/Global)-level data</u>

- Describe the overall mortality of patients hospitalized with COVID-19 by time epoch (week/month);
- Describe the proportion of patients who died by time epoch in relation to the publication of therapeutic guidelines for COVID-19;
- Describe and compare the proportion of patients who died by time epoch (week/month) and by WHO region;
- Assess how the proportion of patients who died by time epoch changes with respect to treatment availability and wealth level;
- Assess how the proportion of patients who died by time epoch changes according to wealth level and prevalence of opportunistic infections at sites, in relation to the publication of therapeutic guidelines regarding steroid administration for COVID-19 ;

IF AVAILABLE: Analyzes based on patient-level data

- Describe proportion of patients hospitalized with COVID-19 receiving corticosteroids, remdesivir, IL6RB, JAK inhibitors, monoclonal antibodies, with respect to severity levels (note that this list will evolve over time);
- Describe the proportion of patients receiving these therapies (see list above) by time epoch (week) in relation to the publication of therapeutic guidelines for COVID-19 and severity levels;
- Compare the proportion of patients receiving these therapies (see list above) by time epoch, by WHO region and severity levels.
- Assess the overall risk of opportunistic infections (i.e. mycobacterial, fungal infections... list TBD) in patients hospitalized with COVID-19;
- Describe the proportion of patients hospitalized with COVID-19 with opportunistic infections by week in relation to the publication of therapeutic guidelines for COVID-19
- Compare the proportion of patients with opportunistic infections by time epoch and by WHO region
- Analyze statistically the relation between mortality in patients hospitalized with COVID-19 and administered treatment.

Planned Statistical Analyses, Methodology and Representation

Analyzes based on site(hospital/countries/WHO regions/Global)-level data

- Overall frequencies of key variables and frequencies stratified by region (tables, heat-map).
- Curves of mortality over time (weeks) by region
- Interrupted time series models will be used to assess mortality rates by regions as a function of time, in relation to the publication of therapeutic guidelines for COVID-19. In cases where interventions are not expected to have an immediate effect on the mortality rate, models will not include a “shifted intercept” term, but will otherwise. Models will include parameters to account for interaction effects of, in turns,: region, treatments availability, wealth level, and region’s prevalence of opportunistic infections.

IF AVAILABLE: Analyzes based on patient-level data

- Overall frequencies of key variables and frequencies stratified by region (tables, heat-map);
- Curves of treatment administration rates over time (weeks), by region if data from various regions are available.
- Logistic regression (mixed, if several data from several sites available) models
- Random forests and support vector machines to explore the importance of administered treatments (either before time x or through the course of) in the predictability of mortality in patients hospitalized with Covid-19.

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 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.

References

Please list any relevant references.