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
Variation in management and outcomes of hospitalized patients with COVID-19 among low-, middle- and high-income countries

Version: (Date: Day/Month/Year)
9/11/2021

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Introduction

Coronavirus Disease 2019 (COVID-19) is caused by a novel coronavirus (SARS-CoV-2) that was first identified in December 2019 in Wuhan, China. The virus rapidly spread to other provinces in China and other countries such that WHO declared COVID-19 as a pandemic on 11 March 2020. COVID-19 has resulted so far in more than 235 million cases as of October 8, 2021.[1] The disease causes significant morbidity and mortality with a case fatality rate close to 2%.[1] The mortality is much higher in patients who develop critical illness and organ failure.[2, 3] The numbers of deaths per million population differ widely across countries[4, 5] and even among hospitals in the same country.[6] Factors that may explain this variability are related to differences in patient and nonpatient or system characteristics.[4-6] Inherent patient characteristics that may affect outcome include age and frequency of comorbidities, such as hypertension, diabetes and obesity.[4, 7] Nonpatient or system characteristics include the population density, public health level, healthcare infrastructure (i.e., number of hospital beds per population), COVID-19 policies (i.e., social distancing and closures) and socioeconomic characteristics.[4, 5] These factors are difficult to measure in clinical studies, but may be reflected by the provided treatments as well as the setting for providing such treatments (i.e., in ICU versus outside the ICU). A study that evaluated variation in mortality among 70 US hospitals found that acute physiology (49%), demographics and comorbidities (20%), and socioeconomic status (12%) were the largest contributors to observed variation in mortality, with strain (9%), hospital quality (8%), and treatments (3%) contributing a total of approximately 20% to variation in mortality.[6]

Before it became a pandemic, the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) launched a dedicated COVID-19 Clinical Characterization Protocol and Case Report Forms in January 2020 as well as a free data management platform for researchers from different parts of the world to enter and upload their clinical data. It has so far data on >500000 hospitalized patients with COVID-19 with contributions by 788 sites in 62 countries. Cases are from countries of different income classification as per the World Bank classification.

Because of differences in nonpatient characteristics, we hypothesize that patients from high-income versus low-and middle-income countries vary in the provided care and outcomes.

Research Plan

Summary of Research Objectives
-To compare the management and outcomes of hospitalized patients with COVID-19 between low-, middle- and high-income countries in the whole cohort and in the subgroup of critically ill patients

Proposed Target Population
Adult (≥ 18 years) patients with COVID-19 confirmed by SARS-CoV-2 rt-PCR admitted between March 2020 and present and hospitalized in the centers participating in the ISARIC database.

Clinical Questions/Descriptive Analyses
1. What are the differences in characteristics of hospitalized patients (key demographic variables and admission tests) among low-, middle- and high-income countries? 2. What are the differences in characteristics of critically ill patients with respect to key demographic variables among low-, middle- and high-income countries? 3. What are the differences in management elements of hospitalized patients among low-, middle- and high-income countries? 4. What are the differences in management elements of critically ill patients among low-, middle- and high-income countries? 5. What are the differences in outcomes of hospitalized patients among low-, middle- and high-income countries? 6. What are the outcomes of critically ill patients among low-, middle- and high-income countries?

Planned Statistical Analyses, Methodology and Representation
The following data will be noted: Patient characteristics data: demographic information (age, sex, height, weight, body mass index, geographic (LMIC vs. non LMIC), race, days from first symptom onset to hospital admission and to ICU admission, amongst others); -comorbid conditions (Hypertension, chronic cardiac disease, chronic kidney disease, chronic pulmonary disease, diabetes, asthma, obesity, smoking, tuberculosis, congenital heart disease, malnourishment and others); 4C ISARIC mortality score[8]

Admission data: Vital signs; Laboratory values (daily worse value): PaO_2, PCO_2, pH, HCO_3, Base excess, WBC count, hemoglobin, lactate, ferritin, INR, PT, APPT, Fibrinogen, D-Dimer, CRP, LDH, Troponin and others.

Management data: initial admission location (ward, HDU/ICU), treatments (Antivirals, length of invasive and non-invasive mechanical ventilation, high flow nasal oxygen, corticosteroids, tocilizumab, anticoagulation, convalescent plasma, antibiotics, inotropic/vasopressor support, neuromuscular blockade, prone positioning, renal replacement therapy, ECMO and others)

Outcome data: inhospital complications (classified as respiratory, neurologic, cardiovascular, gastrointestinal and systemic) hospital mortality, ICU mortality, DNR, length of stay in ICU, length of stay in hospital, tracheostomy, discharge home versus nursing facility.

Continuous variables in these data will be expressed as median with interquartile range (IQR), and categorical variables as counts with percentages.

Patients will be grouped according to the country into three groups: low-, middle- and high-income countries.

Multivariable logistic regression models will be constructed to identify associations between patient characteristics (potential confounders, including patient demographics and existing comorbidities) and each of ICU admission and hospital mortality. P-value for interaction between the low-, middle- and high-income countries will be reported.

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

Data retrieval, preliminary analysis: December 2021-January 2022

Data interpretation: February 2022

First manuscript draft: March-May 2022

Final manuscript: June 2022

Manuscript submission: June 2022

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