



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-, upper-middle- and high-income countries
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Working Group Chair (name, ORCID ID, email, institution, country)
Yaseen M. Arabi, MD, FCCP, FCCM (corresponding author) ORCID: 0000-0001-5735-6241 College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, and Intensive Care Department, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia ICU2, Mail Code 1425 PO Box 22490 Riyadh 11426, Saudi Arabia 00966118011111 x 18855 arabi@nqha.med.sa
¹Working group co-chair (name, ORCID ID, email, institution, country)
Hasan M Al-Dorzi, MD ORCID: 0000-0002-3772-8949 College of Medicine, King Saud bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center and Intensive Care Department, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia ICU2, Mail Code 1425 PO Box 22490 Riyadh 11426, Saudi Arabia aldorzih@yahoo.com

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.

Mohammad Bosaeed, MD
College of Medicine, King Saud bin Abdulaziz University for Health Sciences and King
Abdullah International Medical Research Center and Intensive Care Department,
Infectious Diseases Department, Ministry of National Guard Health Affairs, Riyadh, Saudi
Arabia

bosaeedmo@NGHA.MED.SA

Statistician (name, ORCID ID, email, institution, country)

Omar Debasi, PhD
King Abdullah International Medical Research Center and Intensive Care Department,
King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi
Arabia

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 non-patient 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) Non-patient 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 >800000 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.

The objective of this study is to evaluate the differences in processes of care and outcomes among hospitalized patients with COVID-19 in low-middle, upper middle and high income countries.

Participatory Approach

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
To compare the processes of care and outcomes among hospitalized patients with COVID-19 in low-middle-, upper-middle- and high-income countries.
Proposed Target Population
Adult (≥ 18 years) patients with hospitalized with confirmed or suspected COVID-19 between March 2020 and present and hospitalized in the centers participating in the ISARIC database.
Clinical Questions/Descriptive Analyses
<ol style="list-style-type: none"> 1. What are the differences in characteristics of hospitalized patients (key demographic variables and admission tests) low-middle-, upper-middle- and high-income countries? 2. What are the differences in management elements of hospitalized patients among low-middle-, upper-middle- and high-income countries? 3. What are the differences in outcomes of hospitalized patients among low-middle-, upper-middle- and high-income countries? 4. Does the 4C ISARIC mortality score(8) perform similarly in the low-, middle- and high-income countries?
Planned Statistical Analyses, Methodology and Representation
<p>The following data will be noted:</p> <p><u>Patient characteristics data:</u> Demographic information (age, sex, height, weight, body mass index, days from first symptom onset to hospital admission and to emergency admission, amongst others); Comorbid conditions (diabetes, chronic pulmonary disease including asthma, hypertension, chronic cardiac disease, chronic renal disease, Liver disease, obesity, tuberculosis, rheumatologic disease, chronic neurological disease, any malignancy including leukemia, lymphoma, or solid tumors congenital heart disease, malnourishment and others); 4C ISARIC mortality score(8)</p>

Admission data: Vital signs (highest temperature, heart rate, respiratory rate, systolic BP, diastolic BP, AVPU); laboratory values (daily worse value): PaO₂, PCO₂, pH, HCO₃, base excess, WBC count, differential, hemoglobin, hematocrit, platelets, glucose, blood urea nitrogen, creatinine, bilirubin, lactate, ALT, AST, ferritin, INR, PT, APPT, fibrinogen, IL-6, D-Dimer, CRP, LDH, sodium, potassium, procalcitonin, troponin

Diagnostics: PCR testing for COVID

Management data: Admission location (ward, HDU/ICU), Intervention (any oxygen therapy, invasive and non-invasive mechanical ventilation, high flow nasal oxygen, neuromuscular blockade, High-frequency oscillation ventilation, ECMO, nitric oxide, prone positioning, tracheostomy, renal replacement therapy, vasopressor use, blood transfusion, antivirals or COVID 19 targeted agents, corticosteroids, anticoagulation, convalescent plasma

Outcome data: Hospital mortality, length of stay in hospital, discharge home versus nursing facility.

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

Continuous variables in these data will be expressed as mean and standard deviation or median with interquartile range (IQR) based on normality testing, and categorical variables as counts with percentages. Missing data will be reported.

To assess if the 4C ISARIC mortality score(8) performs similarly in the low-, middle- and high-income countries, standardized mortality rates will be calculated for the different groups with 95% confidence interval.

We will compare patient characteristics and processes of care across the three groups.

We will compare outcomes across the three groups.

Multivariable logistic regression models will be fitted to estimate associations between dichotomous hospital mortality and the country income groups (low-income countries being the reference). The covariates that will be entered in the model will include patient demographics (age, gender) and comorbidities. We will divide the cohort into four quartiles to evaluate the change of outcomes over time. The results will be presented as odds ratio with 95% confidence interval.

We will perform subgroup analysis (hospital mortality) for patients < 65 years and ≥ 65 years.

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. We will include data from countries with >50 reported cases. Variables with greater than 30% missingness will be excluded from analysis. Where appropriate, imputation will be performed using Multiple Imputation by Chained Equations (MICE). Imputation will not be done for outcome variables.

References

1. World health Organization. WHO Coronavirus (COVID-19) Dashboard. available at <https://covid19.who.int/>. Accessed on October 10.
2. Armstrong R, Kane A, Kursumovic E, Oglesby F, Cook TM. Mortality in patients admitted to intensive care with COVID-19: an updated systematic review and meta-analysis of observational studies. *Anaesthesia*. 2021;76(4):537-48.
3. Macedo A, Gonçalves N, Febrá C. COVID-19 fatality rates in hospitalized patients: systematic review and meta-analysis. *Annals of epidemiology*. 2021.
4. Hradsky O, Komarek A. Demographic and public health characteristics explain large part of variability in COVID-19 mortality across countries. *European journal of public health*. 2021;31(1):12-6.
5. Asfahan S, Shahul A, Chawla G, Dutt N, Niwas R, Gupta N. Early trends of socio-economic and health indicators influencing case fatality rate of COVID-19 pandemic. *Monaldi Archives for Chest Disease*. 2020;90(3).
6. Churpek MM, Gupta S, Spicer AB, Parker WF, Fahrenbach J, Brenner SK, et al. Hospital-level variation in death for critically ill patients with COVID-19. *American journal of respiratory and critical care medicine*. 2021(ja).
7. Booth A, Reed AB, Ponzo S, Yassaee A, Aral M, Plans D, et al. Population risk factors for severe disease and mortality in COVID-19: A global systematic review and meta-analysis. *PLoS one*. 2021;16(3):e0247461.
8. Gupta RK, Harrison EM, Ho A, Docherty AB, Knight SR, van Smeden M, et al. Development and validation of the ISARIC 4C Deterioration model for adults hospitalised with COVID-19: a prospective cohort study. *The Lancet Respiratory Medicine*. 2021;9(4):349-59.