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
Exploring associations between ethnicity, in-hospital complications and COVID-19 outcomes in the United Kingdom, Brazil, and South Africa
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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

The severe acute respiratory syndrome coronavirus (SARS-CoV-2) has led to over 455 million confirmed cases of COVID-19 resulting in over 6 million recorded deaths (1). Hospital admission is estimated to be necessary for 10-20% of adults with COVID-19 as a consequence of progression to severe and critical disease (2). In response to the global pandemic, several cohort studies have described the clinical features of hospitalised patients with COVID-19 in order to better characterise the disease and the likelihood of severe outcomes (3–6).

Some studies to date have explored the disproportionate impact of COVID-19 over ethnic minority groups (7), including how admission to critical care, use of invasive mechanical ventilation (IMV) and in-hospital mortality vary by ethnicity. In a study of 260 hospitals across the UK, Harrison, *et al* (8, preprint), contribute to this area and conclude that hospitalised patients in the UK from ethnic minorities are more prone to enter critical care and more in need of IMV than patients categorised as White. In particular, among the considered ethnicities, South Asians (hazard ratio 1.19, 1.05 to 1.36) experienced an increased risk of death. In contrast, Yates, *et al* (9), observe that ethnicity and obesity are correlated with a higher likelihood for the aforementioned outcomes, with correlations strongest in patients in the UK who are categorised as Black. However, further comparative analysis between diverse settings would be needed to evaluate the effect of COVID-19 over different ethnicity.

As a result of international collaboration, ISARIC (International Severe Acute Respiratory and Emerging Infections Consortium) has supported the standardised collection of data globally. From the last available ISARIC COVID-19 Clinical Data Report (10), data have been provided by 64 countries with the largest contributors being South Africa (55.1%) and the UK (33.8%). Moreover, from the Latin America and Caribbean region, Brazil obtained data from almost 10,000 patients (Figure 1). Therefore, given the diversity of population and socioeconomic characteristics within these countries, this project would involve a comparative analysis including ISARIC-associated cohort data from the United Kingdom, South Africa and Brazil.

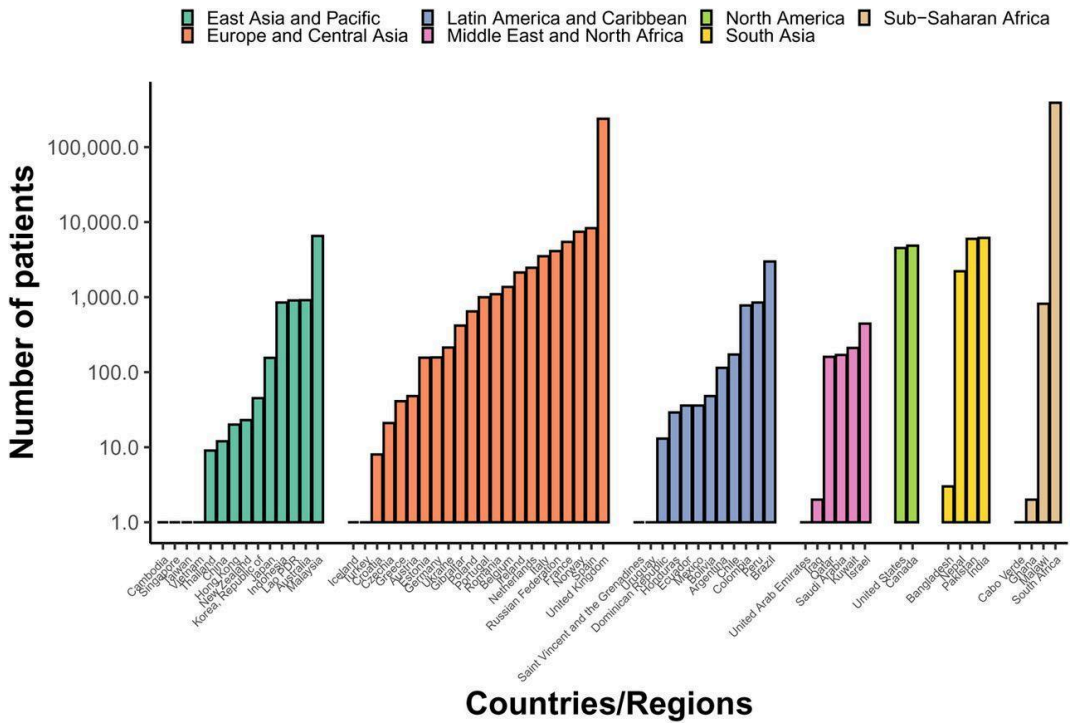

Figure 1: Distribution of patients by region and country. ***From ISARIC Clinical Characterisation Group (2022)***

To support clinicians in the triage and management of patients with COVID-19, the ISARIC WHO CCP-UK derived and validated two pragmatic risk stratification tools during the first pandemic wave of hospital admission in the UK, the 4C Deterioration model and the 4C Mortality Score (11,12). The former elaborates a model for in-hospital clinical deterioration, whereas the latter aims to design a prognostic score for in-hospital mortality. These models enable early detection of patients that are most at risk of severe outcomes (e.g., deterioration or death) and may contribute to an efficient allocation of available resources and treatments. While both models have been further validated to demonstrate their consistent performance during the second pandemic wave of hospital admission in the UK (13), validation of their performance in ISARIC-associated cohorts outside of the UK and evaluation with the addition of patient factors, such as ethnicity and income deprivation would be of critical importance.

Based on these premises, the role of ethnicity in COVID-19 outcomes in different settings is worth further exploration. This document details the initial analysis plan for publication on a subset of COVID-19 patients enrolled in the global ISARIC cohort between 11th March 2020 (e.g., WHO declares a global pandemic) and 17th March 2022.

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

1. To compare the similarities/differences of COVID-19 characteristics (e.g., symptoms on admission, comorbidities, demographics) in patients hospitalised in Brazil and South Africa versus the United Kingdom and across different ethnicities within all three countries. The observations will be adjusted for age, background vaccination rate wave periods (as a proxy for predominant circulating variant), comorbidities, complications and demographics. Moreover, given the potential importance of regional differences within each of the countries, particularly with respect to ethnic diversity, we would consider country regions to be included in sub-group analyses.

   As part of the background research for this objective, relevant studies of hospitalised COVID-19 patients from low and middle-income country settings will be reviewed and findings will be compared to findings from the ISARIC database. If data are sufficient from this review, a meta-analysis of relevant risk factors may be conducted at a later stage.

2. To assess whether risk factors driving mortality and in-hospital deterioration (defined as any requirement of ventilatory support or critical care, or death (12)) are consistent in diverse settings and across ethnicity, using data from hospitalized adult patients in Brazil, South Africa and the United Kingdom.
   a. Validation of the 4C prognostic models using ISARIC data from the Brazil and South Africa databases, taking into account emerging SARS-CoV-2 variants and change in uptake of COVID-19 vaccines across the period of analysis*.

* Different models will be evaluated including ones where variables are common across all study settings and ones where variables are only available for 2 of 3 sites.

Proposed Target Population

Objective 1

The analysis will include participants of all ages who have been enrolled in respective ISARIC cohorts from the UK, Brazil and South Africa and admitted to hospitals with confirmed or highly suspected SARS-CoV-2 infection.

Objective 2

The analysis will include adults (age ≥18 years) who have been enrolled in respective ISARIC cohorts from the UK, Brazil and South Africa and admitted to hospitals with confirmed or highly suspected SARS-CoV-2 infection.

For both objectives, the proposed period of analysis will be for data collected from March 2020 to March 2022.

Clinical Questions/Descriptive Analyses

Objective 1

Univariable/descriptive analyses

1. What are the characteristics of the patients with respect to demographic variables (stratified by country and ethnicity and adjusted for potential confounders like age and sex)?
2. What are the characteristics of the patients with respect to comorbidities, including when stratified according to country and ethnicity?
3. What are the characteristics of the patients across ethnicities with respect to complications*, including when stratified according to country and ethnicity?
    a. What proportion of patients requires transfer to Intensive Care Unit or High Dependency Unit (ICU/HDU)?
    b. What proportion of patients requires use of invasive mechanical ventilation (IMV)?
4. What is the vaccination coverage in the different ethnic groups and the considered countries?
    a. What were the background vaccination rate and predominant circulating SARS-CoV-2 variant in the country?
5. When stratified by ethnic group and country, what proportion of patients are: discharged alive or died (e.g., status at 28 days)?
    a. What is the case-fatality ratio (CFR) in the considered cohort, adjusted for age group? How have the probabilities of death and discharge varied over time?
    b. Does the probability of outcomes (e.g., access to ICU/HDU; use of IMV; risk of death) change over time and with the emerging of new variants?

* Complications are defined “as organ-specific diagnoses occurring alone or in addition to any hallmarks of COVID-19 illness” (14)

Multivariable Analysis

1. What risk factors (e.g., pre-existing comorbidities; background vaccination rate) predict poor outcomes, stratified by ethnicity?
    a. Is there an association between demographic variables and complications (e.g., access to ICU/HDU; use of IMV) or risk of death?
    b. Is there an association between pre-existing comorbidities and complications (e.g., access to ICU/HDU; use of IMV) or risk of death?
    c. Is there an association between complications and risk of death, when stratified by ethnicity?

Objective 2

1. Is the performance of the ISARIC 4C Deterioration model and the 4C mortality score consistent in Brazil and South Africa?
2. Does the performance of the prognostic models vary across time and through the different pandemic periods (as a proxy for predominant circulating variant), and with respect to different ethnic groups?

Planned Statistical Analyses, Methodology and Representation

Clinical question	Planned statistical analyses	Planned representation in manuscript(s)
Univariable/Descriptive analyses		
Objective 1		
Considered comorbidities: diabetes, chronic pulmonary disease, chronic kidney disease, asthma, malignant neoplasm, chronic cardiac disease, chronic neurological disorder, HIV/AIDS, tuberculosis, smoking, obesity, and hypertension.		
Considered complications*: complex respiratory (bacterial pneumonia, acute respiratory distress syndrome [ARDS], pneumothorax, pulmonary embolism, and pleural effusion), neurological (meningitis, encephalitis, seizure, and stroke), cardiovascular (thromboembolism, heart failure, myocarditis, endocarditis, arrhythmia, cardiomyopathy, myocardial ischaemia, and cardiac arrest), acute kidney injury, liver dysfunction, pancreatitis, and gastrointestinal haemorrhage, and other systemic complications (coagulopathy, disseminated intravascular coagulation, anaemia, and bloodstream infection).		

*Complications are defined “as organ-specific diagnoses occurring alone or in addition to any hallmarks of COVID-19 illness” (14)

Outcomes: the primary outcome is in-hospital mortality (e.g., status at 28 days). Admission to Intensive Care Unit or High Dependency Unit (ICU/HDU), and use of invasive mechanical ventilation (IMV) are considered secondary outcomes. For temporal analysis, we will consider time to death, discharge or censoring.

1. What are the characteristics of the patients with respect to demographic variables (stratified by country and ethnicity and adjusted for potential confounders like age and sex)? 2. What are the characteristics of the patients with respect to comorbidities, including when stratified according to country and ethnicity? 3. What are the characteristics of the patients across ethnicities with respect to complications, including when stratified according to country and ethnicity? a. What proportion of patients requires transfer to ICU/HDU? b. What proportion of patients requires IMV? 4. What is the vaccination coverage in the different ethnic	Continuous variables will be evaluated through median (IQR), mean (standard deviation). Categorical variables will be calculated with proportions and percentages with 95% confidence interval. Comparisons between groups will be made using chi-square test (e.g. categorical variables), Welch's t test, ANOVA (e.g. continuous variables) for normally distributed data. Non parametric tests (e.g. Kruskal-Wallis test, Mann-Whitney U test) will be considered according to data distribution. Questions 4-5 Cox proportional hazard models will be used to assess the effect of the covariates on survival. For question number 5 we will evaluate the effect of covariates on hospital outcome. Estimates will be expressed by hazard ratio (95% confidence interval, P-value). Question 5. CFR will be calculated using the modified Kaplan-Meyer method (15) for the entire cohort and the specified subgroups.	● Summary tables ● Bar plots (categorical variables) ● Box plots (continuous variables distributions) ● Kaplan-Meier plots comparing different ethnic groups

groups and the considered countries? a. What were the background vaccination rate and predominant circulating SARS-CoV-2 variant in the country? 5. When stratified by ethnic group and country, what proportion of patients are: discharged alive or died (e.g., status at 28 days)? a. What is the case-fatality ratio (CFR) in the considered cohort, adjusted for age group? How have the probabilities of death and discharge varied over time? b. Does the probability of outcomes (e.g., access to ICU/HDU; use of IMV; risk of death) change over time and with the emerging of new variants?		
<u>Multivariable Analyses</u>		
Objective 1		

1. What risk factors (e.g., pre-existing comorbidities; background vaccination rate) predict poor outcomes, stratified by ethnicity? a) Is there an association between demographic variables and complications (e.g., access to ICU/HDU; use of IMV) or risk of death? b) Is there an association between pre-existing comorbidities and complications (e.g., access to ICU/HDU; use of IMV) or risk of death? c) Is there an association between complications and risk of death, when stratified by ethnicity?	1. The likelihood of the associations will be explored using logistic regression (OR and 95%CI). To compare models we will use Akaike Information Criterion (AIC), whereas ROC curves will be used to test discriminative ability. Moreover, Hosmer-Lemeshow "goodness of fit" test will be used to further assess performance in terms of calibration. <u>Predictor variables</u> ● Demographic (age, gender, ethnicity, country) ● Signs and symptoms (as indicated in the ISARIC case report form) ● Comorbidities ● Complications ● Variants of concern (VOC) ● Vaccination status ● Number of doses <u>Outcome variables</u> ● Access to ICU/HDU ● Use of IMV ● Mortality	● ROC curves ● OR plots
Objective 2		
Outcomes: discrimination and calibration of prognostic models for in-hospital deterioration (e.g., admission to Intensive Care Unit or High Dependency Unit (ICU/HDU), use of invasive mechanical ventilation (IMV) or death) and in-hospital mortality.		
1. Is the performance of the ISARIC 4C Deterioration model and the 4C mortality score consistent in Brazil and South Africa?	1-2 Discrimination will be quantified through the C-statistic for each prognostic model. Calibration will be assessed by	● Forest plots ● Summary tables ● ROC curves

2. Does the performance of the prognostic models vary across time and through the different pandemic periods (as a proxy for predominant circulating variant), and with respect to different ethnic groups?	performing calibration slopes, calibration-in-the-large , and calibration plots. Clinical utility will be evaluated by using decision curve analysis. Sensitivity analysis will be used to evaluate models' performance across time, countries and ethnic groups. Patients will be classified into different groups according to the distinct waves of the pandemic. We will then calculate the area under the receiver operating characteristic curve (AUC) with 95% confidence intervals for each wave. <u>Predictor variables</u> ● Demographic (age, gender, ethnicity, country) ● Number of comorbidities ● Respiratory rate (per min) ● SpO2(%) ● Room air or oxygen ● Radiographic infiltrates ● Glasgow coma scale ● Lymphocytes (x10^9 /L) ● Urea (mmol/L) ● C-reactive protein (mg/L) ● Oxygen received ● Systemic steroids received	
*Limitations: We acknowledge that laboratory results and clinical measures might not be available in an adequate number of participants due to missing data, thus limiting our ability to		

further evaluate the performance of the prognostic models. If the data available are not sufficient to perform the analysis, we will critically evaluate and compare the type of missing data between countries.

Handling of Missing Data

A 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 that lack sufficient data to allow for any useful analysis to be performed on them, including alternative non-parametric techniques. Type of missingness shall be considered including whether missingness occurs at random; follow-up with sites will be conducted if appropriate. Where appropriate, imputation will be performed using Multiple Imputation by Chained Equations (MICE). Actions taken would depend on the type of missingness and the relevance of the variable to the analysis under consideration.

Other Information

Dissemination of research findings will occur collaboratively with investigators through publication in peer-reviewed journals, presentations at international conferences and in line with ISARIC's policies for results dissemination at national and sub-national levels.

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