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:

<table>
<thead>
<tr>
<th>Title of proposed research</th>
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<tr>
<td>Utility of measures of oxygenation for COVID-19 case management and outcome</td>
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</table>

Version: (Date: Day/Month/Year)

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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

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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.
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

Background and rationale

Analyses of the ISARIC dataset (Mark Pritchard, 4 October 2020) (ISARIC Clinical Characterisation Group, 2020) show that

(1) Current case-definitions based on fever and/or respiratory symptoms correctly identify only a proportion of confirmed covid-19 at the time of hospital admission, especially at the extremities of age amongst the young and the elderly. Fever (68%), cough (68%) and shortness of breath (63%) were the most prevalent symptoms. Their prevalence was greater among patients aged 30–60 years (respectively 79%, 78%, 66%), and lower in children (≤18 years: 68%, 47%, 22%) and older adults (≥70 years: 61%, 62%, 61%).

Legend: Age- and sex- specific odds of meeting clinical definitions among patients admitted to hospital with Covid-19, stratified by age and sex. Each plot is the result of a logistic regression with a composite
group of symptoms as an outcome. Fixed effects of age in ten-year bands (baseline group 50–60 years) and sex are shown in black boxes with 95% confidence intervals. The size of each square is inversely proportional to the variance of the log odds ratio, so larger boxes indicate greater certainty. Clustering by country is included as a random intercept and heterogeneity is depicted by circles showing the median odds ratio. ‘Respiratory symptom’ is any of cough, rhinorrhea, shortness of breath, sore throat or wheeze. Patients missing a symptom included in any criteria are excluded from all four plots.

(2) Overall, less than one-third (27789/88846, 31.3%) present with SpO2 <94%, and even fewer in younger and middle-aged patients

(3) At the same time, about two-thirds of the patients hospitalized will require at some point during hospital stay oxygen supplementation. Specifically, 58593/87271 (67.1%) patients received some degree of oxygen supplementation: of these, 13142/58593 (22.4%) received NIV and 10083/58593 (17.2%) IMV. These proportions increase substantially for patients in ICU: 14794/15786 (93.7%) received oxygen supplementation, of whom, 7576/14794 (51.2%) received NIV and 9531/14794 (64.4%) IMV. We anticipate the following main scenarios (others might be discovered on investigating the dataset):
   a. Patient is normoxic on admission and never requires oxygen
   b. Patient is normoxic on admission but later becomes hypoxic and requires oxygen – NB: SpO2 may be recorded or not.
   c. Patient is hypoxic on admission and is given oxygen on admission – NB: important to distinguish between SpO2 taken prior to or while already on O2 therapy.

(4) These respiratory markers are being used to guide patient management decisions.

**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
Research Plan

Summary of Research Objectives

The primary objective is to assess the utility of measures of oxygenation as a predictor of poor outcome in Covid-19. A secondary objective is to assess the utility of measures of oxygenation to guide patient management decisions. An additional secondary objective is to evaluate the ROX index, S/F94 rox and ROX-HR in a subset of patients.

Proposed Target Population

The analysis population includes enrolled participants who met all eligibility criteria.

Eligibility

Patients must have lab-confirmed SARS-Cov2 infection and baseline SpO2 recorded

Baseline patient characteristics

Key variables on admission will be:
- Age
- Sex
- Time from onset of illness
- Respiratory symptoms
- Respiratory rate
- SpO2 (a subset analysis for those with also PaO2, and/or FiO2)
- FiO2 – to be derived from:
  - If room air 0.20
  - If on Oxygen therapy:
    - Type of oxygen therapy
    - Flow (L/min)
- Heart rate
- Symptoms at presentation including chest pain, cough, shortness of breath
- Comorbid conditions including asthma, chronic pulmonary disease alone or combined with severe respiratory conditions, current/former smoking
- Cardiovascular conditions including chronic cardiac disease, hypertension, TB, Obesity. These will be evaluated either alone or in combination with the respiratory conditions.

Follow-up variables

Variables during hospitalization:
- O2 therapy (type, time and duration)
- Steroid treatment

Clinical Questions/Descriptive Analyses

Clinical questions

The main clinical question is to understand the association between measures of oxygenation at the time of hospitalization and outcome, as well as their role in patient management.
To do so, we will study respiratory conditions (including respiratory symptoms, respiratory rate, pulse oximetry, arterial gas analysis) at presentation and how they evolve over time and determine the needs for oxygen therapy, of which type, and when.
As the RECOVERY trial showed the survival advantage of receiving steroids depending on severity / O2 therapy needs, steroid treatment will be considered as well to help interpret outcomes.
We will then study the relationship between these parameters and outcome, accounting for explanatory variables.

Outcome definition
The outcome of interest is whether the patient was discharged alive or died. The time to death, discharge or censoring will be the endpoint.
A secondary outcome will be the need for O2 therapy and type.

Analysis methods
We will analyse time to death and discharge with respect to the SpO2 at admission. SpO2 will be first considered as continuous. The functional form of the relationship could be studied by using fractional polynomials. A 2 and 3-category transform will then be tested.

To start with the modeling, a proportional hazard model will be used to evaluate the time to death or discharge with respect to SpO2 and other potentially confounding variables. Competing risks between death and discharge will be considered. The survival procedure of the Cox model will be used to fit the proportional sub-distribution hazards model.

The proportional hazard assumption will be tested. In case it is not respected, time dependence of the SpO2 or other variables will be accounted for. Model assessment will be performed through cumulative sums of Martingale residuals (and plotted) allowing to check for the functional form of SpO2. A frailty model will then be tested by including country and/or study design as random effects.
A ROC curve analysis will be carried out from the final survival model to evaluate the predictive accuracy of the SpO2 and other selected variables.

Sensitivity analyses evaluating whether characteristics at admission such as O2 supplementation would potentially introduce biases in the results will also be carried out.
Visual summary of Analyses

On admission (BL)

- Key variables: RR, SpO2, (PaO2), (FiO2) (P/F, S/F, S/P)
- Descriptive analysis
  - Tables: mean (Std), median (IQR), min/max; boxplots by age group & sex for FR_Y vs FR_N
- Demographics: age, sex – fig see Mark’s paper
- Duration of illness – mean (std), median etc.
- Admitted to ward or HDU/ICU – 2x2 table
- O2 therapy (any) on admission – 2xn table

During hospitalisation

- O2 Rx Yes
  - F+R Yes
  - F+R No
  - *And by type of O2 Rx
- Utility of measures of BL oxygenation to inform on need for O2 therapy
- Logistic model, ROC curves
- AUC (individually (RR, SpO2, PaO2) combined (P/F, S/F, S/P)

Outcome

- Discharged alive
- Dead
- Association between BL oxygenation and outcome
- Survival model
- Association between BL oxygenation + O2 therapy and outcome
- Additional variables for model: Time from admission to outcome
- Ward vs HDU/ICU
- Country
- Epi week?

Sankey plots: Admission → in-hospital → outcome

Planned Statistical Analyses, Methodology and Representation

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameter</th>
<th>Type</th>
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<tbody>
<tr>
<td>Fixed effects</td>
<td>Intercept</td>
<td></td>
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<tr>
<td></td>
<td>Age</td>
<td>Continuous</td>
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<tr>
<td></td>
<td>Sex</td>
<td>Categorical: M, F, Other</td>
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<tr>
<td></td>
<td>Duration of illness</td>
<td>Continuous</td>
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<tr>
<td></td>
<td>Clinical &amp; respiratory: fever, cough, shortness of breath</td>
<td>Categorical, Categorical, Categorical</td>
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<tr>
<td></td>
<td>Co-morbidities: COPD</td>
<td>Categorical</td>
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<tr>
<td></td>
<td>Respiratory rate</td>
<td>Continuous</td>
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<tr>
<td></td>
<td>SpO2</td>
<td>Continuous, Categorical e.g. Binary: &lt;95%</td>
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<tr>
<td></td>
<td>PaO2</td>
<td>Continuous</td>
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<td></td>
<td>SpO2/FiO2</td>
<td>Continuous</td>
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<td></td>
<td>Oxygen therapy</td>
<td>Categorical: O2 supplementation; NIV or equivalent; IMV can be multiple</td>
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<tr>
<td></td>
<td>Time to initiation of O2 therapy</td>
<td>can be multiple; can be D0</td>
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<tr>
<td></td>
<td>Steroid therapy</td>
<td>Categorical</td>
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<tr>
<td>Random effects</td>
<td>Original study</td>
<td>Categorical</td>
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<td></td>
<td>Design of the study (if relevant)</td>
<td>Categorical</td>
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<tr>
<td>Clinical Question</td>
<td>Planned statistical analyses</td>
<td>Planned representation in manuscript(s)</td>
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<td><strong>Univariable/descriptive analyses</strong></td>
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| 1) What are the characteristics of patients (respiratory rate, SpO2 [a subset analysis for those with also PaO2, and/or FiO2] with respect to key demographic variables (age, sex,) and respiratory parameters (fever + respiratory symptoms)? | Descriptive analysis tables:  
- Mean (std), median (IQR), min/max  
- N (%)  
Boxplots by 10y age group and sex for fever+respiratory symptoms versus no symptoms | ● Bar plots – for displaying the frequencies of categorical variables  
● Box plots – for summarizing distributions (quantitative outcome variables only)  
● Summary tables |
| 2) What proportion of patients are discharged alive, have died? | | |
| 3) What proportion of patients require different levels of O2 supplementation? | | |
| **Multivariable analyses** | | |
| 1. What duration of respiratory symptom predict need for O2 therapy in hospitalized patients with COVID-19? | Logistic model of oxygenation measures / no measure with respect to respiratory rate and SpO2 or PaO2 at admission  
Roc curves and evaluation of AUC individually for RR, SpO2 and PaO2  
Competing risks model / frailty competing risk Model.  
**Predictor variables on admission:**  
- Age (continuous and categorical [10-y age-bands])  
- Sex (categorical)  
- Duration of illness (continuous)  
- Clinical & respiratory: (categorical): fever, cough, short of breath  
- Respiratory rate (continuous; and categorical? E.g.>25 breaths/min in <50 yo; >30 breaths/min >50 yo in adults)  
- SpO2 (continuous and categorical (<95%))  
- (PaO2)  
- SF (SpO2/FiO2)  
- SF941  
- ROX2 [(S/F)/RR] = 4.88  
- ROX-HR 3 [(ROX/HR)*100]  
- Comorbid conditions  
- Oxygen therapy [categorical: O2 supplementation; NIV or equivalent; IMV]) – or exclude those on O2 at presentation? Or treat it as below  
**Predictor variables during hospitalization (for question 2):**  
- Oxygen therapy [categorical: O2 supplementation; NIV or equivalent; IMV] – can be multiple  
- Time of initiation of O2 therapy – can be multiple; can be D0. NB: not available for patients without daily forms; duration of O2 therapy should be reported for most patients though.  
- Steroid therapy | ● Forest plots  
● ROC curves  
● Cross tabulations of different variables |
| 2. What measures of lung functions / oxygenation predict need for O2 therapy in hospitalized patients with COVID-19? | | |
| 3. What measures of lung functions / oxygenation predict poor outcome in hospitalized patients with COVID-19? | | |
| **Outcome variables** | | |

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1. SF94 = (SpO2/FiO2)  
2. ROX = [(S/F)/RR]  
3. ROX-HR = [(ROX/HR)*100]
Confidence intervals and p-values
For all analyses, a two-sided p-value of <0.05 will be used to determine statistical significance for all analyses. Confidence intervals will be calculated at the 95% level. Where appropriate, Benjamini–Hochberg corrected P values <0.05 and a false discovery rate threshold of 0.1 will be used to adjust for multiple comparisons.

Handling of Missing Data
Observations missing at random will be modeled directly through the multiple imputations method by chained equations (MICE).

Other Information
Initial outputs expected within three months from final approval of SAP.

References

1 Brown & Baillie, personal communication (paper in preparation): exclude SpO2 >=94%

2 Roca et al, Am J Respir Crit Care Med Vol 199, Iss 11, pp 1368–1376, Jun 1, 2019


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