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
Prevalence of use and outcomes of Non-invasive oxygenation strategies as first-line treatment of COVID-19 respiratory failure
Version: (Date: Day/Month/Year)
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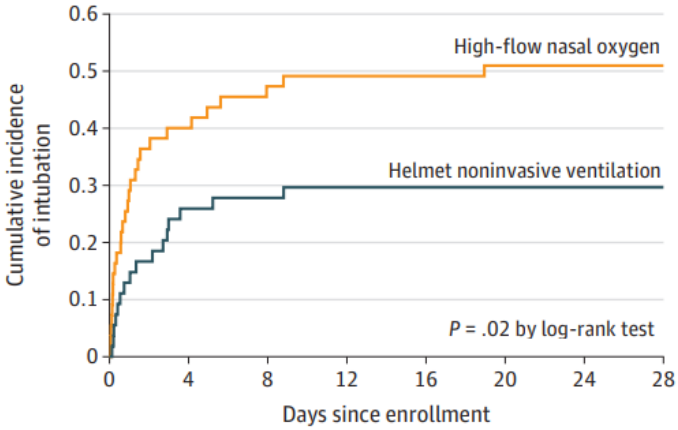
Final draft SAPs will be circulated to all ISARIC partners for their input with an invitation to participate. ISARIC can help to set up collaborator meetings; form a working group; support communications; and accessing data. Please note that the details of all approved applications will be made publicly available on the ISARIC website. Please complete all sections of this form fully and return to ncov@isaric.org

Introduction

Hypoxemic respiratory failure is the most frequent life-threatening complication of COVID-19. The optimal initial respiratory support for these patients is controversial, and different approaches have been applied with variable success rates.[1-3] Non-invasive oxygenation strategies (high-flow nasal oxygen, helmet or face mask non-invasive ventilation and continuous positive airway pressure) compared with standard oxygen therapy have been shown to be capable of preventing endotracheal intubation in patients with mild hypoxemia.[4] However, the role of non-invasive oxygenation strategies in patients with moderate-to-severe hypoxemia has long remained unclear, because the failure rate is high and patients intubated after a failing trial of noninvasive support show increased mortality, mostly due to delayed intubation and patient self-inflicted lung injury. Because high-flow nasal oxygen is simple to use and has clinical and physiological effects, it is often adopted as the first-line intervention for respiratory support in patients with hypoxemia and is widely applied in patients with COVD-19. Helmet non-invasive ventilation has recently been advocated as an alternative for the management of acute hypoxemic respiratory failure.

Cumulative Incidence of Intubation Over Time in the Helmet Noninvasive Ventilation and High-Flow Nasal Oxygen Groups to Day 28



No. at risk

High-flow nasal oxygen	55	34	30	28	28	27	27	27
Helmet noninvasive ventilation	54	41	39	38	38	38	38	38

The hazard ratio for endotracheal intubation in the helmet noninvasive ventilation is 0.49 (95% CI, 0.27-0.89). Follow-up was completed to 60 days after randomization for all patients.

A recent multicenter randomized controlled trial compared COVID-19 patients receiving high flow nasal oxygen versus helmet non-invasive ventilation.[5] Helmet non-invasive ventilation did not result in a reduced duration of respiratory support. However, it was associated with improved oxygenation and dyspnea, reduced rate of endotracheal intubation, and increased days free of invasive ventilation at 28 days from randomization (fig.1 fig.2). Following the Berlin Definition for Acute Respiratory Distress Syndrome (ARDS), hypoxemia severity is traditionally classified with the ratio between arterial partial pressure of oxygen (PaO_2) and inspired oxygen fraction (FiO_2), as mild (PaO_2/FiO_2 ratio of 201 to 300 mmHg), moderate (PaO_2/FiO_2 ratio of 101 to 200 mmHg) and severe (PaO_2/FiO_2 ratio ≤100 mmHg).[6]

In this ancillary analysis of the ISARIC database, we propose to assess the prevalence of use and clinical outcomes (rate of failure) of noninvasive oxygenation strategies among COVID-19 patients included in the ISARIC databes and exibiting hypoxemic respiratory failure.

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
We aim to describe the current global practice in the treatment of Covid-19 respiratory failure and to determine the proportion of the patients managed with non-invasive oxygenation strategies (high-flow nasal oxygen, helmet or face mask non-invasive ventilation and continuous positive airway pressure (CPAP)) in the intensive care unit. We aim to assess the rate of treatment failure (need for endotracheal intubation) and clinical outcome (hospital mortality) in the overall cohort of patients, and in the subgroup of patients with PaO2/FiO2>150 mmHg and ≤150 mmHg. Subgroup analyses will be performed for patients treated in the ICU or in a non-ICU environment. We also aim to stratify patients based on the different interfaces adopted for NIV (helmet vs oronasal mask vs full face mask). Secondary objective will be to compare patients who received noninvasive support or direct invasive mechanical ventilation as first-line treatment of hypoxemic respiratory failure due to COVID-19, after propensity score matching based on age, sex, PaO2/FiO2, BMI, and eventually, if data are available, the use of dexamethasone, remdesivir, anti-IL-6 agents.

Proposed Target Population
The analysis population includes enrolled participants who met all eligibility criteria. Eligibility Eligible patients will be selected from the population admitted to the emergency department (ED) and COVID-19 medical wards as well to the Intensive Care Unit ➢ Age > 18 yo; ➢ A baseline $PaO_2/FiO_2 \leq 300$; ➢ Adoption of one of the following strategies: high-flow nasal oxygen, helmet or face mask non-invasive ventilation and continuous positive airway pressure; ➢ Patients with a confirmed (PCR positive on nasopharyngeal swab) SARS-COV-2 infection. For the propensity matched comparison, a sample of patients treated with first-line invasive mechanical ventilation will be used as comparator. Baseline patients' characteristics ➢ Age ➢ Sex ➢ BMI ➢ SAPS II ➢ SOFA score ➢ Major comorbidities ➢ Time from onset of illness to meeting the inclusion criteria ➢ Concomitant medications such as steroid therapy, immunomodulatory therapy, antibiotics or antiviral therapy ➢ Respiratory symptoms ➢ Time from hospitalization to meeting the inclusion criteria ➢ Richmond Agitation-Sedation Scale (RASS) and Glasgow Coma Score (GCS) ➢ Type of non-invasive oxygenation strategy (NIV or CPAP or HFNO or conventional oxygen) ➢ Type of interface (nasal cannula or helmet or facemask) ➢ For patients receiving NIV ventilatory settings ➢ For Patients receiving HFNO FiO2 and Flow (lpm) ➢ Heart Rate, Systolic Blood Pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) ➢ Use of vasopressors ➢ Use of sedatives ➢ Temperature ➢ Need for renal replacement therapy

- Parameters at the day of ARDS onset (pH, PaO2, PaCO2, FiO2, Base Excess)

Follow up variables

- Need for endotracheal intubation
- Respiratory support free days at day 28 and day 60
- Invasive mechanical ventilation free days at day 28 and day 60
- Type of non-invasive oxygenation strategy (NIV or CPAP or HFNO or conventional oxygen)
- Type of interface (nasal cannula or helmet or facemask)
- Noninvasive ventilation ventilatory settings
- FiO2 and Flow (lpm) during high flow nasal oxygen
- ABG (pH, PaO2, PaCO2, FiO2, Base Excess)
- Invasive ventilation rate
- Length of mechanical ventilation (invasive and non-invasive)
- Need for a tracheostomy
- Mortality rate (in-intensive care unit and in-hospital)
- Length of stay (in-intensive care unit and in-hospital)
- Acute Kidney Injury requiring renal replacement therapy

  [The KDIGO guidelines define AKI as follows:
  - ●Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 micromol/L) within 48 hours, or
  - ●Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior seven days, or
  - ●Urine volume <0.5 mL/kg/hour for six hours

  Following KDIGO guidelines AKI is staged as follows:
  - ●Stage 1 – Increase in serum creatinine to 1.5 to 1.9 times baseline, or increase in serum creatinine by ≥0.3 mg/dL (≥26.5 micromol/L), or reduction in urine output to <0.5 mL/kg/hour for 6 to 12 hours.
  - ●Stage 2 – Increase in serum creatinine to 2.0 to 2.9 times baseline, or reduction in urine output to <0.5 mL/kg/hour for ≥12 hours.
  - ●Stage 3 – Increase in serum creatinine to 3.0 times baseline, or increase in serum creatinine to ≥4.0 mg/dL (≥353.6 micromol/L), or reduction in urine output to <0.3 mL/kg/hour for ≥24 hours, or anuria for ≥12 hours, or the initiation of kidney replacement therapy, or, in patients <18 years, decrease in estimated glomerular filtration rate (eGFR) to <35 mL/min/1.73 m^2.

- Need for extracorporeal membrane oxygenation (ECMO)
- Evidence for barotrauma (Clinical manifestations of barotrauma are multiple interstitial emphysema, pneumothorax, pneumomediastinum, subcutaneous emphysema)
- Duration of intravenous sedation

- Duration of vasopressor infusion
- Duration of steroid therapy
- Duration of antibiotics

Clinical Questions/Descriptive Analyses
The main clinical question is to assess the prevalence of use and clinical outcomes of noninvasive oxygenation strategies in COVID-19 patients.
Planned Statistical Analyses, Methodology and Representation
For continuous variables, we will report median with interquartile range or mean ± SD, and for categorical variables, we will report proportions. Student's t, F Wilcoxon rank sum, or Kruskal-Wallis, chi-square, or Fisher tests will be used to compare groups as appropriate. Multivariable Cox proportional hazards models will be applied to investigate the relationship between covariates and outcomes (endotracheal intubation and intubation). Propensity score matching method will be used to evaluate the possible different treatment effects on survival. To compare patients who received noninvasive support or direct invasive mechanical ventilation as first-line treatment of hypoxemic respiratory failure due to COVID-19, 1:1 propensity score matching based on age, sex, PaO2/FiO2, BMI, use of dexamethasone, use of remdesivir, use of antiIL-6 agents will be performed. For the propensity matched comparison, a sample of patients treated with first-line invasive mechanical ventilation will be used from the ISARIC database as comparator.
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) Grasselli G, Zangrillo A, Zanella A, et al; COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy.JAMA. 2020;323(16):1574-1581.

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3) Franco C, Facciolongo N, Tonelli R, et al. Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related pneumonia. Eur Respir J. 2020; 56(5):2002130.

4) Ferreyro BL, Angriman F, Munshi L, et al. Association of Noninvasive Oxygenation Strategies With All-Cause Mortality in Adults With Acute Hypoxemic Respiratory Failure. JAMA.

5) Grieco DL, Menga LS, Cesarano M, et al. Effect of Helmet Noninvasive Ventilation vs High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure: The HENIVOT Randomized Clinical Trial. *JAMA.* 2021;325(17):1731–1743.

6) The ARDS Definition Task Force. Acute Respiratory Distress Syndrome: The Berlin Definition. *JAMA.* 2012;307(23):2526–2533.

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