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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

Title of proposed research
Extracorporeal Membrane Oxygenation for COVID-19 Respiratory Distress Syndrome: a ISARIC Risk Factor Analysis
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Introduction

Due to SARS-CoV-2 rampant spread worldwide, on March 11, 2020, coronavirus disease 2019 (COVID-19) was labeled a pandemic by the World Health Organization (WHO).
Interim WHO guidelines, the Extracorporeal Life Support Organization (www.elso.org), the Paris-Sorbonne University Hospital Network analysis, the Surviving Sepsis Campaign and others recommend administering venovenous (VV) extracorporeal membrane oxygenation (ECMO) to eligible patients with COVID-19 related severe respiratory distress syndrome at expert centers.
SARS-CoV-2 causes respiratory failure due to alveolar damage. The rate of severe respiratory distress syndrome ranges from 15% to 30%. Currently, no specific therapy exists. The ELSO registry counts more than 2,611 respiratory ECMO having been implanted worldwide, showing an overall in-hospital mortality rate of 45% and patients discharge alive to home or acute rehabilitation of 23%. Contrary to preliminary literature results that indicated dismal outcomes with 84%–100% mortality of patients with COVID-19 given ECMO, the current estimated 31% probability of day 60 mortality for ECMO-treated patients is similar in the EOLIA trial, the prospective LIFEGARD registry, the Paris-Sorbonne University Hospital Network analysis, the running ELSO registry survey and the recent Italian Society for Cardiac Surgery task force report.

This document details the initial analysis plan for publication on a subset of COVID-19 patients in the global cohort in the ISARIC database, as of 20 Aug 2020. There are currently 44 countries (as of 20 AUG 2020) contributing data and these have so far contributed data on 102,038 patients. This data will represent the global experience of the first 6 months of this pandemic particularly focusing on of VV and/or ECMO treated COVID-19 patients.
The current analysis would have the aim to weight the efficacy and safety of ECMO support in COVID-19 patients.

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
Specific Aim 1: Descriptive analysis of all ECMO treated COVID-19 patients. Analysis of Outomes, ECMO-related Adverse Events, and Mortality rate while on ECMO running.

We intend to query the ISARIC and ECMOCARD database, specifically patients who required intensive care unit admission for COVID-19 and upgraded to ECMO treatment. We will then identify the following variables:

- Demographic data: age, sex, height, weight, body mass index, geographic, race, days from first symptom onset to hospital admission and to ICU admission, amongst others
- Symptoms: history of fever, shortness of breath, cough, fatigue, confusion among others.
- Comorbidities: Hypertension, chronic cardiac disease, chronic kidney disease, chronic pulmonary disease, diabetes, asthma, obesity, smoking, tuberculosis, congenital heart disease, malnourishment and others.
- Treatments: Antivirals, length of invasive and non-invasive mechanical ventilation, corticosteroids, convalescent plasma, antibiotics, prone positioning, renal replacement therapy, neuromuscular blockade, inotropic/vasopressor support and others.
- Vital signs (daily worse value): temperature, heart rate, respiratory rate, oxygen saturation, systolic blood pressure, diastolic blood pressure, capillary refill, and others.
- Laboratory values (daily worse value): PaO2, PaO2/FiO2, PCO2, pH, HCO3, Base excess, WBC count, hemoglobin, lactate, ferritin, INR, PT, APPT, Fibrinogen, D-Dimer, CRP, LDH, Troponin, and others.
- Time, type and parameters of ventilation (both for non-invasive and invasive mechanical ventilation), … PEEP, Tidal Volume, Compliance, tracheostomy, pre-ECMO.
- ECMO setting (VV, VVA, VA), type of ECMO cannulation, type of circuit, oxygenator, cannulae sizing, pump and ECMO technology adopted, ECMO flows, type on mechanical ventilation on ECMO, IABP on ECMO, tracheostomy on ECMO, proning on ECMO, Cytosorb on ECMO, volume balance on ECMO, acute kidney injury on ECMO, Renal Replacement Therapy on ECMO, multiple organ failure on ECMO, superinfections on ECMO, sepsis on ECMO, bleeding on ECMO, transfusions on ECMO, pulmonary embolism on ECMO, lung complications on ECMO, cerebral stroke on ECMO, leg ischemia on ECMO, ECMO duration, weaning from ECMO, repeat ECMO need, exitus on ECMO, exitus after ECMO.
- Type of anticoagulation management while on ECMO.
- Type of medications, antivirals, antibiotics, corticosteroids, inotropes, vasoactive drugs on ECMO.
- ICU stay (time), adverse events in ICU (post-ECMO), exitus in ICU (post-ECMO).

Specific Aim 2: To predict pre-ECMO and on-ECMO variables for ECMO-related Adverse Events and Mortality (Risk Factors) of COVID-19 pts.

Specific Aim 3: Splitting Analysis of Outcomes into two populations, if available, in terms of pediatric and adult COVID-19 populations.

All above to weight the efficacy and safety of ECMO support in COVID-19 patients.

Proposed Target Population

All ISARIC COVID-19 patients (both pediatric and adult populations) who required ICU

level care and escalated to VV and/or VA ECMO support. All above to identify the risk variables associated with ECMO-related Adverse Events and Mortality on-ECMO in ISARIC COVID-19 patients dataset.

Clinical Questions/Descriptive Analyses

Questions:

1. What pre-ECMO, on-ECMO and ICU variables are associated with the ECMO-related Adverse Events (AEs) in COVID-19 patients?
2. What pre-ECMO, on-ECMO and ICU variables are associated with mortality while on ECMO support in COVID-19 patients?
3. What is the strength of the different variables in their association with the ECMO-related AEs and Mortality on-ECMO in COVID-19 patients?

Analysis:

- Primary end-point (primary study outcome): COVID-19 patients Mortality while on ECMO running.
- Secondary end-point (secondary study outcomes): Covid-19 ECMO-related Adverse Events. e.g.: cerebral stroke, lung complications, severe acute kidney injury (AKI), renal replacement therapy (RRT) need, multiple organ failure (MOF), bleeding events, superinfections, sepsis, confirmed pulmonary embolism (PE), mechanical ventilation duration, and length of intensive care unit (ICU) stay.
- For all outcomes, survivors and non-survivors will be compared.

Planned Statistical Analyses, Methodology and Representation

Continuous variables will be tested for normality with Shapiro–Wilk's test and reported as means with standard deviation (SD) or as medians with interquartile range (IQR).
To compare continuous variables between survivors and non-survivors, Student's t-test
for unpaired data or Wilcoxon–Mann-Whitney U test will be used.
Categorical variables will be reported as counts and percentages and compared by Pearson $\chi 2$ analysis.
All variables will be compared between survivors and non-survivors by univariate analysis, and those with a $p < 0.05$ were entered into a multivariable model.
Binary logistic regression will be used to identify risk factors for mortality. As a final step, a parsimonious model will be constructed. Bootstrapping in 1,000 samples will be used to correct both estimators and 95% confidence limits. Model discrimination was evaluated using area under the receiver operating characteristic curves.

R-studio version 1.1.463 (2009–2018) and SPSS 24.0 (SPSS, Inc, Chicago, IL) will be used for all statistical analyses. All tests will be two-tailed, and $p \leq 0.05$ will be

set as the criterion for statistical significance.
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

We have established an institutional group dedicated to this project from Bologna University at S. Orsola Hospital, IRCCS Bologna, Italy, a participating ISARIC center:

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2. Davide Pacini, MD, PhD, Cardiothoracic Surgery Department
3. Sofia Martin-Suarez, MD, PhD, Cardiothoracic Surgery Department
4. Gregorio Gliozzi, MD, Cardiothoracic Surgery Department
5. Massimo Baiocchi, MD, Anesthesiology Department
6. Daniela Di Luca, MD, Anesthesiology Department
7. Elisa Cerchierini, MD, Anesthesiology Department

Our research plan is to complete the project in a 12-week time frame from data acquisition to initial deliverable completion. Our academic product goals are a minimum of: 1 publication and 1 research abstract.

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