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
Development of predictive analytics model for need of extracorporeal support in COVID-19
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

The novel coronavirus (SARs-CoV2) and associated disease COVID-19 have placed previously unimaginable demand on the medical system both in resource rich and resource limited settings. The most resource intense and comprehensive support for patients afflicted with COVID-19 is extracorporeal membrane oxygenation (ECMO). It serves a role for the most critically ill patients suffering from life-threatening cardiac and/or respiratory failure. ECMO functions as an artificial heart and/or lung, removing carbon dioxide, supplementing oxygen to a patient's blood, and providing life-sustaining oxygen delivery.

The decision to place a patient on ECMO is one that takes place after standard therapies such as steroids, mechanical ventilation, and prone positioning among others have failed. However, this decision is not one that can be taken lightly, as not only does it require a multidisciplinary team frequently composed of surgeons, intensivists, nurses, perfusionists - for its initiation and daily use, as well as up to 1:1 nursing. In addition, ECMO use itself is associated with risks to the patients and significant morbidities. The decision to deploy ECMO is often complicated by the need to balance the risks to the patients with the potential benefits. This is amplified in times of resource limitations and stress to the healthcare system.

During a pandemic it is critical to be cognizant of the high resources required to place and maintain patients on ECMO. Current guidelines do not recommend commissioning new ECMO centers even during the pandemic and preferential use in patients whom are likely to have favorable outcomes[1]. They further recommend early preferential transfer of suitable ECMO candidates to regional ECMO centers, acknowledging decisions to transfer late may make patients too unstable for transport. While lives can be saved by moving patients to regional ECMO centers when available, the decision on when to do so remains opaque. Current recommendations are only on the basis of expert opinion regarding P:F ratios[2] and would often require transport of many patients who ultimately never require ECMO, further straining resources during the pandemic. As with the understanding of the natural course and complications of COVID-19 infection continue to evolve, the short and long-term outcomes for COVID-19 patients supported on ECMO is not yet clear. A recent Lancet trial[3] demonstrated nearly 40% mortality in 1035 patients requiring ECMO for COVID-19, and it is well known to increase the risk of neurological complications[4] such as seizure, and ischemic and hemorrhagic stroke.

More than 10 months into the pandemic, there remains difficulty in predicting who will require ECMO and incredible resource burden at both smaller regional centers and large academic centers alike. Even within high volume ECMO centers, there remains a lack of clarity on the ability to predict which patients will require ECMO, often causing unexpected resource strain even within high resource institutions.

We plan to construct a model to aid in the prediction of which COVID-19 patients are most likely to necessitate the use of ECMO utilizing the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) database. We hypothesize that a predictive model can help predict the requirement for ECMO initiation 24-48 hours prior to cannulation. This would provide benefits to patients; identifying patients who are high risk for requiring additional resources, as well as patients who may be suitable for transfer from institutions not capable of supporting the high resource requirement that ECMO entails or lacking the requisite expertise of high volume ECMO centers. There would be additional benefit to providers, identifying appropriate local resource allocation and which clinical scenarios may pose the highest risk for healthcare personnel exposure during invasive procedures. Lastly, healthcare systems overall would benefit, when resource demand can more adequately be predicted, during the extreme resource prioritization conditions posed by a pandemic.

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 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: To predict the necessity for ECMO support utilizing variables 24-48 hours prior to ECMO initiation.

We will analyze the demographics, therapeutics, laboratory values, vital signs, for all COVID-19 ICU patients, as well as change in these values associated with the binary outcome of necessitating ECMO support.

Specific Aim 2: Develop, validate and test a machine learning model for predicting the need for ECMO at various time windows using a large international database.

In parallel with specific aim 1, we will develop a model and validate it on holdout data to analyze the ability to predict ECMO need.

Specific Aim 3: Test the developed model in a local, holdout dataset, using a simulated real-time approach, and evaluate the decision alert rate.

In addition to testing the model on holdout data from the international ISARIC database, local Barnes Jewish Hospital and St. Louis Children's Hospital data will be used to back validate the model's accuracy in predicting need for ECMO. Previous ECMO scoring models and alerts have only been measured by overall accuracy which can limit their clinical

significance, analyzing the decision alert rate and testing over various sensitivities will allow our model to be clinically significant to the bedside providers.

Proposed Target Population

All COVID-19 patients who required ICU level care including those who were escalated to ECMO support. In order to identify the variables associated with the provision of ECMO support, it will be imperative to study the general COVID-19 ICU population, including those supported on ECMO. This will allow for further analyses as the number of patients ECMO support would have been suggested for vs the limited guidelines available, like the current ELSO guidelines for example.

Clinical Questions/Descriptive Analyses

1. What pre-ECMO variables are associated with the need for ECMO support in COVID-19 patients?
2. What is the strength of the different variables in their association with the need for ECMO support in COVID-19 patients?
3. Can a predictive analytics model be built to predict the need for ECMO support in critically ill COVID-19 patients?
4. What is accuracy and precision of a predictive analytic model to predict the need for ECMO support in COVID-19 patients?

Planned Statistical Analyses, Methodology and Representation

Specific Aim 1:

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

- Demographic data: age, sex, height, weight, body mass index, geographic (LMIC vs. non LMIC), 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, PCO2, pH, HCO3, Base excess, WBC count, hemoglobin, lactate, ferritin, INR, PT, APPT, Fibrinogen, D-Dimer, CRP, LDH, Troponin and others.

2. Using the identified variables, we will identify factors associated with the need for ECMO support in the 24-48 hours prior to ECMO initiation.
3. Given the lack of international agreed upon eligibility criteria for providing ECMO support. We plan to identify patients at "extreme" spectrums for different demographics and co-morbidities (as age, BMI amongst others). These cohorts will be planned for during the subset analysis in order to build the most generalizable model. Additionally, we plan to identify patients from high income vs low income countries and from high volume vs low volume centers, experience vs. inexperienced (new) ECMO centers for matching during the analysis.
4. We are planning for patient matching as addressed above and to compare outcomes, mainly survival. We believe this, amongst other sub-analyses, will provide the ability to generate more than one high impact publication from this study.

Specific Aim 2:

Our strategy will be then to create a model to predict the outcome of requiring ECMO within 24 hours based on the identified variables by:

1. Multivariate logistic regression
2. Machine learning methods (random forest, gradient boosting machine (GBM))

We will leverage our significant experience in developing clinical predictive models[5] and early warning systems[6-11].

We are planning on utilizing PPV in addition to F1 scores to measure of precision and recall during the model building. When benchmarking a model, reporting AUROC only will leave the model susceptible to rare event bias, with this in mind we will also be reporting area under precision recall curve (AUPRC), which avoids the rare event bias of simply reporting AUROC.

Model evaluation: We will create the model on 80% of the data, leaving a further 20% of the data for holdout testing.

Specific Aim 3:

We will then back validate the model to evaluate its accuracy and precision on:

1. A 20% holdout data on the ISARIC dataset
2. Local institutional data, from both Barnes Jewish Hospital and St. Louis Children's Hospital.

Handling of Missing Data

Despite the large nature of the ISARIC database, a potential problem may be the lack of patients with the necessary outcome. We will employ a set of state-of-the-art methods to avoid model overfitting, handle the imbalance in the dataset, and enhance the interpretability of the predictive model.

1. We will apply feature selection techniques to choose the set of variables that yield optimal predictive performance while avoiding overfitting;

2. We will employ synthetic minority oversampling to creates synthetic outcome samples while under-sampling negative samples.
3. We will develop model interpretation[12] to highlight the most predictive variables associated with the predictive outcomes.

Other Information

We have established an institutional group dedicated to this project from Washington University in St. Louis, St. Louis, MO USA, a participating ISARIC center:

1. Ahmed Said, MD PhD, Assistant Professor, Pediatric Critical Care
2. Neel Shah, MD, Assistant Professor, Pediatric Critical Care
3. Chenyang Lu, PhD, Professor, Department of Computer Science and Engineering
4. Thomas Kannampallil, PhD, Assistant Professor of Department of Anesthesiology and the Institute for Informatics; Associate Chief Research Information Officer at Washington University in St. Louis

Our research plan is to complete the project in a 10-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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