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
Coagulopathy and thrombosis among COVID-19 patients: Variation by geographical location and healthcare setting.
Version: (Date: Day/Month/Year)
10 January 2021
Working Group Chair (name, ORCID ID, email, institution, country)
Matthew Griffee, 0000-0002-4217-4565, Matthew.griffee@hsc.utah.edu, University of Utah/ University of Utah School of Medicine, USA
[1]Working group co-chair (name, ORCID ID, email, institution, country)
Patricia Bozza, 0000-0001-8349-9529, pbozza@gmail.com, Fundação Oswaldo Cruz, Brazil
Statistician (name, ORCID ID, email, institution, country)
Angela Presson, angela.presson@hsc.utah.edu, University of Utah/Division of Epidemiology, USA **Chong Zhang, Chong.Zhang@hsc.utah.edu, University of Utah/Division of Epidemiology, USA**

[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.

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

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 17 Jan 2021. There are currently 64 countries (as of 17 Jan 2021) contributing data and these have so far contributed data on 305241 patients. This data will represent the global experience of the first 12 months of this pandemic.

Coagulation disorders have been observed in prior coronavirus epidemics such as SARS-CoV-1 and MERS-CoV, and a hallmark of the SARS-CoV-2 pandemic is vascular inflammation and endothelial injury leading to both thrombotic and hemorrhagic complications (1-2). Because of the novelty of COVID-19 and the conflicting implications of attempting to avoid both serious thrombosis and serious hemorrhage, guidelines on evaluation and management of COVID-19 patients with coagulopathy have substantial variations (3).

We propose to characterize patients in the ISARIC registry with bleeding, thrombosis, and coagulopathy with an approach that leverages the strengths of the large international registry. Determination of geographic variation in COVID-19 associated coagulopathy observations may provide insight into whether different regions may have different coagulopathy phenotypes. Describing and characterizing the bleeding and coagulopathy seen among COVID-19 patients who are critically ill may help refine risk assessment for the sickest patients. Describing regional variation in practices of anticoagulation may aid in designing prospective clinical trials.

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. Aim 1: To describe bleeding, thrombosis, and coagulopathy among hospitalized patients with COVID-19 who do not require mechanical ventilation, and to compare the frequency of these problems across geographic regions. The frequency will also be compared between high income and low- and middle-income regions. Risk factors for coagulopathy will be identified.

2. Aim 2: To describe bleeding, thrombosis, and coagulopathy among COVID-19 patients who require invasive mechanical ventilation, and to compare the frequency of these problems across geographic regions and between high income regions vs. low- and middle-income regions. Risk factors for coagulopathy will be identified.

3. Aim 3: To describe regional variation (defined by geography and by economic stratification) in anticoagulation treatment practices for COVID-19 patients. Describe the frequency of any anticoagulation, the type of anticoagulation, frequency of anti-platelet use, and how often prophylactic, intermediate, and therapeutic dosing is prescribed.

4. Aim 4: To present coagulopathy lab values associated with bleeding and thrombosis complications.

5. Aim 5: To determine the impact of bleeding, thrombosis, and coagulopathy in patients hospitalized with severe and non-severe COVID-19. The main outcomes of interest are in-hospital mortality and length-of-stay. An exploratory aim is to determine whether use of anticoagulation is associated with survival to discharge, controlling for need for mechanical ventilation.

Proposed Target Population

Aim 1: All hospitalized COVID-19 patients with sufficient data for analysis, excluding patients who require mechanical ventilation.

Aim 2: Patients with COVID-19 who require invasive mechanical ventilation.

Aim 3: All hospitalized patients with COVID-19.

Aim 4: Patients with COVID-19 with complications of bleeding and thrombosis.

Aim 5: Patients hospitalized with COVID-19, stratified according to need for invasive mechanical ventilation, who have complications from thrombosis, bleeding or coagulopathy. The exploratory aim compares patients who are treated with anticoagulation, compared to those who are not anticoagulated.

Clinical Questions/Descriptive Analyses

1. What are the regional differences in the coagulopathy and thrombosis manifestations observed for hospitalized COVID-19 patients who do not require mechanical ventilation? How do coagulopathy manifestations differ in patients in high income regions vs. in patients in low- and middle-income regions? What are demographic, treatment, economic, and location risk factors for coagulopathy?

2. Among COVID-19 patients requiring mechanical ventilation, how often are bleeding, thrombosis, and coagulopathy reported? Are there regional differences in the coagulopathy manifestations of COVID-19 for patients who require mechanical ventilation? Are there differences in coagulopathy manifestations of mechanically ventilated patients in high vs. low- and middle-income regions? What are demographic, treatment, economic, and location risk factors for coagulopathy?

3. How does the use of anticoagulation therapy vary by geographical and economic region?

4. Present key lab values observed in patients with complications of bleeding and thrombosis.

5. What are the effects of coagulopathy complications on length-of-stay and survival? Is there an association between use of anticoagulation and survival?

Planned Statistical Analyses, Methodology and Representation

The predominant methodology is descriptive, except for Aim 5.

Definition of cohorts for Inclusion

Non-Mechanically ventilated cohort: Hospitalized patients with COVID-19 who do not have treatment with mechanical ventilation (Treatment field 348, Invasive ventilation, Critical Care Module 539, Invasive ventilation).

Mechanical ventilation cohort: Patients who do have affirmation in Treatment Instrument of Field 348, or Critical Care Module Field 539, “Invasive Ventilation.”

Population of patients treated with anticoagulation:
Yes to 484, “Heparin” and/or to 567, “Heparin for systemic anticoagulation?”

Population of patients with coagulopathy complications:
Admission signs and Symptoms Instrument, Field 142, Bleeding (Haemorrhage), 1)Yes.

Patients with affirmation of any of the following:
Complications Instrument:

Field	Term
385	Stroke/cerebrovascular accident
389	Coagulation disorder/DIC

390 Pulmonary embolism
394 Gastrointestinal hemorrhage

Follow Up Self-Assessment Survey Instrument:
643 Deep vein thrombosis
644 Stroke or mini stroke/TIA
645 Pulmonary embolism
685 Bleeding

Regions

Frequencies of coagulopathy complications will be compared by region. Proposed regions: Europe, North Africa, Sub-Saharan Africa, Middle East, East Asia, South Asia, West Asia, Latin America, North America.

Economic stratification will be defined based on World Bank classification of countries into low and middle income vs. high income countries. The comparison is coagulopathy complications and anticoagulation practice in low- and middle-income countries, compared to these complications and practices in high income countries.

Aim 1: Describe hospitalized COVID-19 patients with coagulopathy complications who do not require invasive ventilation. Inclusion: Non-mechanical ventilation cohort with one or more of the following presentations:

Instrument	Data Field Number	Term
Admission Signs	142	Bleeding (Haemorrhage)
Complications	385	Stroke/ CVA
Complications	389	Coagulation disorder/ DIC
Complications	390	Pulmonary Embolism
Complications	394	GI Hemorrhage

Follow Up Self-Assessment	643	Deep vein thrombosis
Follow Up Self-Assessment	644	Stroke or mini stroke/TIA
Follow Up Self-Assessment	645	Pulmonary embolism
Follow Up Self-Assessment	685	Bleeding

Description of subjects will include demographics (country, ethnicity, sex, age), Co-morbidities (fields 163-186), treatments (348-357), and outcome (501).

Expected confounding:
Analysis will include evaluation of an expected association of age and length of stay. The frequency of bleeding and coagulopathy complications will be evaluated with

stratification of subjects by age in five-year intervals, with a hypothesis that older age will be associated with increased frequency of coagulopathy complications.

Because mortality and complications of coagulopathy are competing risks, and because of the complex relationships between illness severity, length-of-stay, and complications, a multi-state approach will be used to construct a model of the risk of coagulopathy complications over time (4,5). Hospital length-of-stay and duration of mechanical ventilation will be treated as expected confounders for complications of coagulopathy. In interpretation of characteristics noted for patients with bleeding and thrombosis, it will be important to emphasize that the dates of complications are not included in the case report form. Thus cause and effect inferences may not be possible. For example, a patient who had a pulmonary embolism and also who received therapeutic heparin may have had the embolism first, then heparin started to treat the embolism, but equally may have been on heparin and yet suffered the embolism, representing a treatment failure.

Secondary aim: To account for variation in outcomes *within* each region, compare demographics and outcome, as well as bleeding, stroke, coagulation disorder, and pulmonary embolism within a sample of countries within each region. Countries and sites will be selected in order to create a model of the range of demographics and outcomes across a variety of healthcare settings (high vs. low volume sites, and low/middle vs. high income countries). The purpose is to address whether differences between sites and countries in bleeding and coagulopathy related to COVID-19 are better accounted for by global region or income strata vs. more granular geographic and economic setting.

Aim 2: Describe and characterize mechanically ventilated COVID-19 patients with coagulopathy complications. Inclusion: Mechanical ventilation cohort with one or more of the following presentations:

Instrument	Data Field Number	Term
Admissions Signs	142	Bleeding (Haemorrhage)
Complications	385	Stroke/ CVA
Complications	389	Coagulation disorder/ DIC
Complications	390	Pulmonary Embolism
Critical Care	523-3	Venous thromboembolism
Critical Care	523-10	DIC

Description of subjects will include demographics, co-morbidities, treatments, and outcome. Additional outcome data field is 359, ICU/HDU Duration.

Aim 3: Describe anticoagulation practice variations across regions. Inclusion: Anticoagulation cohort. Relevant data fields:

Instrument	Data Field Number	Term
Daily form	273, 276-285, 329-330	Platelet count, APTT, INR, D-dimer
Medication	484-489	Heparin route, type, dose
Critical Care Module	567-570	Heparin type, role

Critical Care Module	573	Blood transfusion
Critical Care Module	574	Platelet transfusion

Aim 4:.**Present key lab values observed in patients with complications of bleeding and thromboembolism.** Fields for Aim 4.
Population included

Admission Signs	142	Bleeding (Haemorrhage)
Complications	385	Stroke
Complications	389	Coagulation disorder/DIC
Complications	390	Pulmonary embolism
Complications	394	Gastrointestinal hemorrhage

Lab values for patients with coagulopathy:

Instrument	Field	Name
Daily Form	273	Platelet count
Daily Form	278	APTT
Daily Form	285	INR
Daily Form	329	D-dimer
Daily Form	338	Fibrinogen

Quantitative Expressions
Number of non-mechanically ventilated COVID-19 patients with sufficient data for inclusion: N(0)
Number of non-mechanically ventilated COVID-19 patients with coagulopathy complication: N(1)
Number of mechanically ventilated COVID-19 patients with sufficient data for inclusion: N(2)
Number of mechanically ventilated COVID-19 patients with coagulopathy complication: N(3)

Frequency of non-mechanically ventilated patients with coagulopathy complication: N(1)/N(0)
Frequency of coagulopathy complication for patients requiring mechanical ventilation: N(3)/N(2)

Number of COVID-19 patients with data within medications module: N(4)
Number of COVID-19 patients with affirmation of heparin affirmation of field 484: N(5)
Frequency of use of heparin (general population): N(5)/N(4)

Number of COVID-19 patients with data in critical care module: N(6)
Number of COVID-19 patients with affirmation of CCM 567: N(7)
Frequency of heparin (critical care subset): N(7)/N(6)

Number with Intensity of anticoagulation designated therapeutic (checkbox 1 of field 570): N(8)
Number with Intensity of anticoagulation designated prophylactic (checkbox 2): N(9)

Frequency of therapeutic anticoagulation: N(8)/N(6)
Frequency of prophylactic anticoagulation: N(9)/N(6)

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 be 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

Research findings will be analyzed and a manuscript will be composed quickly, within a time frame of weeks, and submitted to a peer-reviewed journal.

References

1. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol. 2020 Jun;127:104362. doi: 10.1016/j.jcv.2020.104362. Epub 2020 Apr 9. PMID: 32305883
2. Dobesh PP, Trujillo TC. Coagulopathy, Venous Thromboembolism, and Anticoagulation in Patients with COVID-19. Pharmacotherapy. 2020 Oct 1. doi: 10.1002/phar.2465. Epub ahead of print. PMID: 33006163.
3. Flaczyk A, Rosovsky RP, Reed CT, Bankhead-Kendall BK, Bittner EA, Chang MG. Comparison of published guidelines for management of coagulopathy and thrombosis in critically ill patients with COVID 19: implications for clinical practice and future investigations. Crit Care. 2020 Sep 16;24(1):559.
4. Wolkewitz M, Cooper BS, Bonten MJ, Barnett AG, Schumacher M. Interpreting and comparing risks in the presence of competing events. *BMJ (Clinical research ed)* 2014; 349: g5060.
5. Hazard D, Kaier K, von Cube M, Grodd M, Bugiera L, Lambert J, Wolkewitz M. Joint analysis of duration of ventilation, length of intensive care, and mortality of COVID-19 patients: a multistate approach. *BMC medical research methodology* 2020; 20: 206.

Working Group Members

- Heidi Dalton heidi.dalton26@gmail.com
- John Fraser fraserjohn001@gmail.com
- Todd Lee todd.lee@mcgill.ca
- Sung-Min Cho csungmi1@jhmi.edu
- Marília Fernandes mariliandreia@sapo.pt
- Arie Zainul Fatoni; ariezainulfatoni@ub.ac.id
- José Pedro Cidade zencidade@gmail.com
- Shinichiro Ohshimo ohshimos@hiroshima-u.ac.jp
- Luis Felipe Reyes luisreyve@unisabana.edu.co
- Ignacio Martin-Loeches imartinl@tcd.ie
- Jordi Rello jrello@crips.es
- Indrek Ratsep indrek.ratsep@regionaalhaigla.ee
- Peta Alexander peta.alexander@cardio.chboston.org
- Dorothea Rosenberger dorothea.rosenberger@hsc.utah.edu