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
Cardiovascular impact in COVID19 patients: a multicenter cohort analysis
Version: (Date: Day/Month/Year)
21st April 2021
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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

COVID19 can be associated with life-threatening organ dysfunction due to septic shock, frequently requiring ICU admission, respiratory and vasopressor support. In fact, hemodynamic instability is registered in almost 35% of COVID19 patients [1-4]. However, evidence has emerged indicating a direct myocardial injury of COVID19, with an associated impact with increased mortality. Therefore, troponin as a well-documented noninvasive biomarker of cardiac injury and myocyte necrosis stand as a possible predictor of a poor outcome in these patients. The independent prognostic value of troponin and other biomarkers on mortality rate, vasopressor-free days and multisystemic dysfunction is still uncertain.

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
• Determine the rate of cardiovascular dysfunction with vasopressor requirements in severe COVID19 patients and its impact on outcomes • Characterize COVID19 patients with cardiovascular dysfunction with vasopressor requirements (See additional notes section below – Note 1) in what concerns previous comorbidities, clinical presentation and survival rates. • Ascertain the prognostic value of troponin levels and hyperlactatemia on vasopressor free days, vasopressor dosage, ventilator free days, SOFA score and Mortality rate.
Proposed Target Population
All patients admitted to Intensive Care with severe COVID19 registered in ISARIC data set.
Clinical Questions/Descriptive Analyses
1. What is the rate of cardiovascular dysfunction with vasopressor requirements within COVID19 patients?

2. What is the impact of cardiovascular dysfunction on outcomes?
3. What are the characteristics of severe COVID19 patients that predict cardiovascular dysfunction with vasopressor requirements?
4. Does troponin levels or hyperlactatemia predict the outcome and survivability of these patients?

Planned Statistical Analyses, Methodology and Representation

1. Overall frequencies of key demographic variables and frequencies stratified by patients' comorbidities.
2. SOFA score at admission, Arrhythmia on admission, daily Minimum Arterial Pressure registered, daily maximum vasopressor dosage, Vasopressor-free days, ventilator-free days, ICU length of stay, KDIGO acute renal failure criteria and Mortality rate will be ascertain and compared between groups
3. Bar plots for displaying frequencies of categorical variables.
4. Linear mixed models and spline regression models (depending its validity on the data completeness on this regard) to ascertain differences between troponin levels and hyperlactatemia levels between patients with cardiovascular dysfunction with vasopressor requirements vs patients without cardiovascular dysfunction with vasopressor requirements.
5. Qui-square test for categorical variables and Kruskal-Wallis and multivariable logistic regression for continuous variables for statistical assessment of outcomes between groups.
6. Kaplan-Meier survival curve and Cox regression test for survivability

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).

Additional Notes

Note 1 - Considering the range of possible form "answers" to the pretended factor of vasopressor support, we would consider:

1. An initial categoric variable with yes/no (to all patients with the need of either of the following treatments: dobutamine, dopamine, epinephrine, Noradrenaline, adrenaline or vasopressin)
2. A further continuous variable reflecting a vasopressor score (a dimensionless variable calculated as follows: dopamine dose (mcg/kg/min) × 1) + (dobutamine dose (mcg/kg/min) × 1) + (epinephrine dose (mcg/kg/min) × 100) + (norepinephrine dose (mcg/kg/min) × 100) + (phenylephrine dose (mcg/kg/min) × 100 + (vasopressin dose (mcg/kg/min) × 100))

This variable will allow us to include the vasopressor in account for a multivariable logistic regression and to compose different vasopressor therapies in a single variable. This vasopressor score has been successfully used in the PROWESS-Shock trial substudy [5]

References

1. Vincent JL, Taccone FS. Understanding pathways to death in patients with COVID-19. Lancet Respir Med. 2020;8:430–2.

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3. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med. 2003;29:530–8.

4. Yader S, L. JJ, S. JA. Cardiac Troponin for Assessment of Myocardial Injury in COVID-19. J Am Coll Cardiol [Internet]. American College of Cardiology Foundation; 2020;76:1244–58.

5. Póvoa P, Salluh JI, Martinez ML, Guillamat-Prats R, Gallup D, Al-Khalidi HR, Thompson BT, Ranieri VM, Artigas A. Clinical impact of stress dose steroids in patients with septic shock: insights from the PROWESS-Shock trial. Crit Care. 2015 Apr 28;19(1):193. doi: 10.1186/s13054-015-0921-x. PMID: 25928214; PMCID: PMC4456711.

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