



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
Acute Kidney Injury in COVID-19
Version: (Date: Day/Month/Year)
6 October 2020
Working Group Chair (name, ORCID ID, email, institution, country)
Dr Marina Wainstein, Staff Specialist Nephrology, Faculty of Medicine, The University of Queensland, Australia QLD 4029 Dr Sally Shrapnel MBBS, BMedSci, MSc (Bioengineering), FRACGP, PhD, Senior Lecturer Data Science, School of Mathematics and Physics, University of Queensland, Australia, s.shrapnel@uq.edu.au
¹Working group co-chair (name, ORCID ID, email, institution, country)
Rolando Claire-Del Granado, Professor of Medicine, Head Division of Nephrology, Hospital Obrero #2 - Caja Nacional de Salud, Universidad Mayor de San Simon School of Medicine, Cochabamba – Bolivia, rclaire@yahoo.com

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.

Statistician (name, ORCID ID, email, institution, country)

Dr Sally Shrapnel, Senior Lecturer Data Science, School of Mathematics and Physics, University of Queensland, Australia, s.shrapnel@uq.edu.au

Samual James MacDonald, Research Assistant, School of Mathematics and Physics University of Queensland, Australia, samual.macdonald@uq.edu.au

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 6 October 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.

As the full spectrum of organ involvement in COVID19-infected patients unravels, kidney disease and acute kidney injury are fast becoming a focus of attention. Close to half of all patients admitted to hospital with COVID 19 have kidney involvement, predominantly in the form of proteinuria or haematuria, and a variable proportion, between 0.5 to 36%, will develop acute kidney injury (AKI) during their hospital stay (1-3). Acute kidney injury is especially common among patients who require mechanical ventilation, with much of its burden observed in the intensive care unit setting and around the time of intubation (1, 4). In this context, development of AKI has been characterised as both a marker of disease severity as well as a negative prognostic indicator, with studies showing lengthier admission times, need for renal replacement therapy and an increased risk of death (pooled odds ratio of 15.27 95% CI 4.82 – 48.36), and (6).

The aetiology of acute kidney injury in these patients is likely to be multifactorial with predisposing factors such as sepsis, hypovolemia and nephrotoxins aggravated by critical volume shifts, cardiac dysfunction, a dysregulated immune response and direct viraemic invasion of renal endothelial and tubular cells (4, 5). Risk factors for AKI identified thus far in COVID19 infected inpatients include older age, black race, diabetes, cardiovascular disease, hypertension, need for mechanical ventilation or vasopressor support as well as evidence of acute kidney disease on admission and severity of pneumonia (1, 3).

Despite a growing body of knowledge on the involvement and behaviour of the kidneys in this disease process, much is yet to be elucidated. To date, studies looking at kidney disease in COVID 19 patients have been limited to single center or regional cohorts mostly from China, Europe or USA, which fail to reflect the global experience of kidney disease, particularly in low middle income countries where the burden of disease may be much higher and the therapeutic resources limited. An analysis of the role of existing kidney disease and pre-admission medications, especially ACE inhibitors, on the incidence, severity and likelihood of recovery from AKI is also lacking in the literature. Closer inspection of the temporal relationship between kidney injury and the broader progression of organ failure may also reveal new culprits for its development as well as guide us towards more timely interventions to prevent it. Thus far, there have been no predictive models developed for AKI in patients with COVID-19. Given the large heterogeneous dataset ISARIC has available there is an opportunity to create externally validated, predictive models for AKI that may generalise to a variety of settings. Of interest is to understand if such models developed on largely UMIC data will generalize to the LMIC setting, where analytic and clinical resources are limited.

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

This analysis has three aims:

- 1) To characterise patients with COVID-19 who develop Acute Kidney Injury (AKI)
- 2) To identify the temporal profile of AKI in patients with COVID-19 throughout the hospital journey
- 3) To develop a predictive machine learning model for AKI in COVID-19, using data from predominantly upper middle-income countries, and externally validate this model in a LMIC setting (Latin America).

Proposed Target Population

The proposed analysis will include adult patients whose data were entered into the ISARIC dataset who were suspected to have COVID-19 at the time of admission.

Research Questions 1) and 2) will include all adult patients who have been identified in the complications module as having experienced Acute kidney injury at any time during their hospital stay. This is defined in the ISARIC CORE module according to the KDIGO criteria as any of:

- Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 $\mu\text{mol/L}$) within 48 hours
- Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days
- Urine volume < 0.5 mL/kg/hour for 6 hours

Research question 3) will also include all adult patients who have been identified in the complications module as NOT having experienced Acute renal injury/Acute renal failure at any time during their hospital stay (as a comparison group to train the classification model).

All adult patients who have been identified in the complications module as UNKNOWN for having experienced Acute renal injury/Acute renal failure at any time during their hospital stay will be censored from this analysis.

The proposed analysis does not allow for censoring of patients who do not yet have an outcome. We therefore need to exclude participants who are still in hospital. To reduce bias from this, we will also exclude patients admitted in the two weeks immediately preceding the data extraction. This also allows for potential delays in entering admission data on to the database, which would otherwise lead to an underestimate of the availability of data to calculate the scores.

Clinical Questions/Descriptive Analyses

1. *What is the incidence of AKI among patients with COVID-19 infection?*

2. *What are the baseline characteristics of patients with COVID-19, stratified by:*

(i) no AKI,

(ii) all grades AKI,

(iii) grade 1 AKI,

(iv) grade 2 AKI,

(v) grade 3 AKI,

(vi) require renal replacement therapy,

Where baseline characteristics include:

a) key demographic variables (age, gender, ethnicity),

b) socioeconomic variables (country income level),

c) clinical variables (co-morbidities, pre-admission medications, laboratory biomarkers on admission),

3. During their hospital stay what proportion of patients that develop AKI, stratified as above:
- a) are admitted to ICU?
 - b) are mechanically ventilated?
 - c) require inotropic support?
 - d) die?
 - e) suffer another complication?
 - f) recover from AKI prior to discharge?
4. What is the length of hospital stay for patients that develop AKI, stratified as above?
5. For those patients who required dialysis and recovered, what length of treatment was required?
6. What is the temporal behaviour of AKI in COVID-19? (ie what day is peak serum creatinine, what is the relationship between development of AKI and intubation/ventilation)?
7. Can we predict the development of AKI vs no AKI in COVID-19 patients?
8. Can we predict the need for RRT in COVID-19 patients?
9. Are predictive models developed for research question's 7 and 8 reliable and robust in a LMIC setting?
10. Type of RRT used
11. Were special filters used (i.e. Cytosorb)
12. Volume overload and AKI, important risk factor for increased mortality, prolonged ventilation, prolonged LOS.

Planned Statistical Analyses, Methodology and Representation

Clinical Question	Planned statistical analyses	Planned representation in manuscript(s)
1) What is the incidence of AKI among patients with COVID-19 infection?	1) Overall frequencies of no AKI, all grades AKI, grades 1, 2, 3 and RRT stratified by socio-economic region.	1) Bar plots – for displaying frequencies
2) What are the baseline characteristics of the study cohort by AKI status? a) key demographic variables (age, gender, ethnicity),	2) Comparisons between no AKI and AKI will use Fisher exact test for categorical variables and nonparametric Kruskal-Wallis test for continuous variables. Comparisons across the	2) Summary tables

<p>b) socioeconomic variables (country income level), c) clinical variables (comorbidities, pre-admission medications, laboratory biomarkers on admission),</p> <p>3. <i>During hospital stay what proportion of patients who develop AKI:</i></p> <p style="padding-left: 40px;">b) are admitted to ICU? c) are mechanically ventilated? d) require inotropic support? e) die? f) suffer another complication? g) have recovered from AKI at discharge?</p> <p>4. <i>What is the length of hospital stay for patients that develop AKI and for those that require RRT?</i></p> <p>5. <i>For those patients who required dialysis and recovered, what was the length of treatment required?</i></p> <p>6. What is the temporal behaviour of AKI in COVID-19? (ie what day is peak serum creatinine,</p>	<p>stages of AKI will use Kruskal-Wallis rank sum test.</p> <p>3. Comparisons between no AKI and AKI will use Fisher exact test for categorical variables and nonparametric Kruskal-Wallis test for continuous variables. Comparisons across the stages of AKI will use Kruskal-Wallis rank sum test.</p> <p>4. summary statistics: observed arithmetic mean, median and SD</p> <p>5. summary statistics: observed arithmetic mean, median and SD</p> <p>6. a) frequencies of peak AKI per day since admission 6. b) probability density function of initial AKI</p>	<p>3. Bar plots – for displaying frequencies.</p> <p>3. Summary table</p> <p>4. Violin plot</p> <p>5. Violin plot</p> <p>6. a) bar graph of frequencies by day since admission 6. b) graph of PDF</p>
---	--	---

<p><i>what is the relationship between development of AKI and intubation/ventilation)?</i></p> <p>7. What are the risk factors for <i>the development of AKI</i> in patients with COVID 19? Can we predict the development of AKI in patients with COVID-19?</p> <p>8. What are the risk factors for the <i>need for dialysis</i> in patients with COVID-19? Can we predict the need for dialysis in patients with COVID-19</p> <p>9. <i>Can models developed for research question's 7,8 be used reliably in a LMIC setting?</i></p>	<p>diagnosis relative to time of intubation</p> <p>7., 8., 9. a) Logistic regression model with adjustment for risk factors that differ between those who developed AKI and those who did not. b) An ensemble machine learning method will be used to provide an alternative predictive model, with feature importance measures to rank input features. Testing on two external data sets: UMIC data and LMIC data.</p> <p><u>Outcome variables</u></p> <p>Questions 7) Development of AKI</p> <p>Question 8) Need for RRT</p>	<p>7., 8., 9 ROCAUC, C statistic, calibration plots for both models, Shapley tree explainer plots for feature ranking</p>
---	---	---

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

Proposed time-line of analysis

1. Characterisation of AKI analysis complete in 4 weeks from acquisition of data, finalization and submission of publication within the following 3 weeks.
2. Temporal progression of AKI complete in 8 weeks from acquisition of data, finalization and submission of publication within the following 3 weeks.
3. Predictive model for AKI complete and externally validated within 12 weeks from acquisition of data, finalization and submission of publication within the following 3 weeks.

Appendix

KDIGO criteria for staging of AKI (6)

Table 2 | Staging of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥0.3 mg/dl (≥26.5 μmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 μmol/l) OR Initiation of renal replacement therapy OR, in patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m ²	<0.3 ml/kg/h for ≥24 hours OR Anuria for ≥12 hours

References

1. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney International*. 2020.
2. Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. *Journal of the American Society of Nephrology*. 2020;31(6):1157-65.
3. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney international*. 2020.
4. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. *The Lancet Respiratory Medicine*. 2020.
5. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *The Lancet*. 2020;395(10234):14178.
6. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Workgroup. KDIGO Clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2(1):1-138.

Working Group Members

- Patrick ROSSIGNOL (Nancy, France): p.rossignol@chru-nancy.fr
- Stephen Knight: stephenknight@doctors.org.uk
- anna.Beltrame@sacrocuore.it
- Carrol Gamble c.gamble@liverpool.ac.uk
- Matthew Cheng; matthew.cheng@mcgill.ca
- Simone Piva; simone.piva@unibs.it
- David Thomson thomson.david@gmail.com
- Christel Arnold-Day, christelday@gmail.com
- François Goehringer (Nancy France). f.goehringer@chru-nancy.fr