ISARIC

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
Potassium in COVID-19 patients admitted to the hospital
Version: (Date: Day/Month/Year)
April 3rd 2021
Working Group Chair (name, ORCID ID, email, institution, country)
On behalf of the French COVID-19 cohort steering committee, a proposal drafted by: Rossignol Patrick (Nancy, FRANCE) Université de Lorraine, Inserm, CHRU Nancy p.rossignol@chru-nancy.fr with Montassier Emmanuel (Nantes, France) ; Hulot Jean-Sébastien (Paris, France) from the FCRIN INI-CRCT network www.inicrct.org
[1]Working group co-chair (name, ORCID ID, email, institution, country)
Jonathan Samuel Chávez Iñiguez, ORCID ID: https://orcid.org/0000-0003-2786-6667, jonarchi_10@hotmail.com, Hospital Civil de Guadalajara, Mexico,
Statistician (name, ORCID ID, email, institution, country)
Sandra Wagner, ; S.WAGNER2@chru-nancy.fr ; CIC-P and FCRIN-INI-CRCT, Nancy, France

[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.

Since reported in late December 2019 from the Hubei province in China, coronavirus disease 2019 (COVID-19) has spread worldwide. Clinical presentation of COVID-19 infection is wide, from asymptomatic infection to severe viral pneumonia with acute respiratory distress syndrome (ARDS). Animal studies found that COVID-19 uses angiotensin-converting enzyme 2 (ACE2) as a cellular entry receptor. ACE2, one of the key enzymes in the renin–angiotensin system (RAS), plays a significant role in regulating fluid and electrolyte balance. Hypokalemia has been described in COVID-19 patients in China and in other countries. In a recent multicenter study, including a total of 594 case patients in whom infection with COVID-19 was confirmed, matched to 594 non-COVID-19 patients (controls), hypokalemia at hospital admission was associated with COVID-19, with an adjusted odds ratio of 1.76 [95% CI, 1.20 to 2.60] (1). In another single-center study including 306 patients, hypokalemia was independently associated with requiring invasive mechanical ventilation during the admission (OR 8.98, 95% CI 2.54–31.74) but not mortality. However, the study only included 18 patients with severe hypokalemia (2). Another monocentric study including 408 patients did not observe that hypokalemia was related to unfavorable outcomes in COVID-19 patients (3). Thus, these discordant findings should be assessed in a larger multicenter study. Importantly, a U-shape relationship has been consistently been found across a variety of populations in the emergent setting (4-5). Whether potassium normalization could be associated with improved outcomes is 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
Main objective: Study the association of baseline potassium and in-hospital death. **Secondary objectives:** A. Prevalence of dyskalemia (hypo/hyperkalemia) at baseline and during the hospitalization B. Determine the factors associated with hypo-hyperkalemia at baseline C. Study the association of repeated potassium measurements and in-hospital death D. Analysis of hospital potassium changes (i.e. potassium normalization) in relation to in-hospital death (6) E. Association of baseline potassium and time to discharge
Proposed Target Population
All hospitalized patients above 15 years with potassium data at baseline
Clinical Questions/Descriptive Analyses
How prevalent is dyskalemia ? What are the clinical factors associated with dyskalemia ? **Are baseline and or in-hospital dyskalemia associated with clinical outcomes ?** Is dyskalemia normalization during the hospitalization associated with (better) clinical outcomes ?
Planned Statistical Analyses, Methodology and Representation
Primary objective: Depending on the shape of the association with in-hospital death, baseline potassium levels will be assessed with splines and/or categorized as severe hypokalemia (under 3 mmol/l), moderate (3-3.4 mmol/l) or mild hypokalemia (3.5–3.9 mmol/L), normal (4 mmol/L-5 mmol/l), mild hyperkalemia (5.1-5.5 mmol/l), moderate hyperkalemia (5.6–6 mmol/l) and severe hyperkalemia (>6 mmol/l). Univariable and multivariable Cox regression models will be fitted on the whole population and then splitted by eGFR strata. The multivariable assessment will consider clinical and biological factors (including eGFR). Sensitivity analyses will be performed in the subgroups of patients ✔ with CKD, ✔ with medications available during the hospitalization. **Secondary objectives:** A. Prevalence of dyskalemia (hypo/hyperkalemia) will be estimated at baseline and during the hospitalization B. Multinomial logistic regression models will be used to determine the factors associated with hypo and hyperkalemia at baseline. C. The association of repeated potassium measurement and in-hospital death will be assessed by time-dependent Cox models D. The changes of potassium will be assessed on 2 consecutive observations during hospitalisation of the same patient. Groups of changes will be created according to potassium evolution of our population (for instance: hyperkalemia to normokalemia

or hyperkalemia to hyperkalemia). Then, the association between those groups and in-hospital death will be evaluated.

A sub-analysis will be performed with the last data of potassium available.

E. Depending on the shape of the association with the outcomes, baseline potassium levels will be assessed with splines and/or categorized as severe hypokalemia (under 3 mmol/l), moderate (3-3.4 mmol/l) or mild hypokalemia (3.5–3.9 mmol/l), normal (4 mmol/l-5 mmol/l), mild hyperkalemia (5.1-5.5 mmol/l), moderate hyperkalemia (5.6–6 mmol/l) and severe hyperkalemia (>6 mmol/l).

Univariable and multivariable assessment (logistic regression models) will be performed on the whole population and then splitted by eGFR strata. The multivariable assessment will consider clinical and biological factors (including eGFR).

Sensitivity analyses will be performed in the subgroups of patients

- ✔ with CKD,
- ✔ with medications available.

Requested data:

- Serum potassium, sodium, creatinine, urea nitrogen at baseline
- Serum potassium and creatinine throughout the hospitalization
- Age, gender, ethnicity
- Comorbidities (Hypertension, Diabetes, Chronic kidney disease, Congestive heart failure)
- Medication if available (Potassium-sparing diuretics, Other diuretics, Angiotensin-converting-enzyme inhibitors, Angiotensin receptor blockers, beta-agonist, Corticosteroids, Antibiotics (i.e. azithromycin), hydroxychloroquin, insulin, potassium supplement)
- Clinical features, Symptoms at hospital admission (e.g. diarrhea, vomiting, severe dehydration)
- ICU admission
- in-hospital death

Handling of Missing Data

A preliminary analysis assured the feasibility of the study, and revealed that >100 000 individuals have potassium data at baseline. Regarding the covariates, the 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

A manuscript reporting the data will be submitted to the consortium within one month after the stats completion.

Working Group Members

FIRST NAME	LAST NAME	EMAIL
Sally	Shrapnel	s.shrapnel@uq.edu.au
Marina	Wainstein	marinawainstein@outlook.com
Matthew	Cheng	matthew.cheng@mcgill.ca
Arie Zainul	Fatoni	ariezainulfatoni@ub.ac.id
Chiara	Robba	kiarobba@gmail.com
Pierre	Tattevin	pierre.tattevin@chu-rennes.fr
Emmanuel	Montassier	emmanuel.montassier@chu-nantes.fr
Ignacio	Martin-Loeches	drmartinloeches@gmail.com
Carlos M.	Luna	cm.luna@gmail.com
Jean-sébastien	Hulot	jean-sebastien.hulot@aphp.fr
Christl	Donnelly	christl.donnelly@stats.ox.ac.uk
Jordi	Rello	jrello@crips.es
Luis Felipe	Reyes	reyeslf@utexas.edu
José Pedro	Cidade	zencidade@gmail.com
Joshua	Solomon	joshua.solomon@mail.mcgill.ca
Lars	Maier	lars.maier@ukr.de
Adam	Nowinski	a.nowinski@igichp.edu.pl
Samuel Bernard Ekow	Harrison	samuel.harrison@kintampo-hrc.org
John	Laffey	john.laffey@nuigalway.ie
Elena Gallego	Curto	elenagallegocurto@gmail.com
Ignacio	Martin-Loeches	imartinl@tcd.ie
Tom	Solomon	tsolomon@liverpool.ac.uk
Benjamin	Lefèvre	b.lefevre@chru-nancy.fr
Jose A	Calvache	jacalvache@unicauca.edu.co
Indrek	Rätsep	indrek.ratsep@regionaalhaigla.ee
Christiana	Kartsonaki	christiana.kartsonaki@dph.ox.ac.uk

Jan Cato	Holter	jcholter@gmail.com
Anna	Beltrame	anna.beltrame@sacrocuore.it
Lucia	Moro	lucia.moro@sacrocuore.it
Dave	Nagpal	Dave.Nagpal@lhsc.on.ca

References

1.deCarvalho H, Richard MC, Chouihed T, Goffinet N, LeBastard Q, Freund Y, Kratz A, M, Masson D, Figueres L, Emmanuel Montassier E. Electrolyte imbalance in COVID-19 patients admitted to the Emergency Department: a case-control study. Intern Emerg Med. 2021 Jan 23; 1-6

2. Moreno-P O, Leon-Ramirez JM, Fuertes-Kenneally L, Perdiguero M, Andres M, Garcia-Navarro M, Ruiz-Torregrosa P, Boix V, Gil J, Merino E; COVID19-ALC Research Group. Hypokalemia as a sensitive biomarker of disease severity and the requirement for invasive mechanical ventilation requirement in COVID-19 pneumonia: A case series of 306 Mediterranean patients. Int J Infect Dis. 2020 Sep 17;100:449-454.

3. Tezcan ME, Dogan Gokce G, Sen N, Zorlutuna Kaymak N, Ozer RS. Baseline electrolyte abnormalities would be related to poor prognosis in hospitalized coronavirus disease 2019 patients. New Microbes New Infect. 2020 Sep;37:100753.

4. Rossignol P, Legrand M, Kosiborod M, Hollenberg SM, Peacock WF, Emmett M, Epstein M, Kovesdy CP, Yilmaz MB, Stough WG, Gayat E, Pitt B, Zannad F, Mebazaa A. Emergency management of severe hyperkalemia: Guideline for best practice and opportunities for the future. Pharmacol Res. 2016;113:585-591

5. Legrand M, Ludes PO, Massy Z, Rossignol P, Parenica J, Park JJ, Ishihara S, AlHabib KF, Maggioni A, Miro O, Sato N, Cohen-Solal A, Fairman E, Lassus J, Harjola VP, Mueller C, Peacock FW, Choi DJ, Plaisance P, Spinar J, Kosiborod M, Mebazaa A, Gayat E. Association between hypo- and hyperkalemia and outcome in acute heart failure patients: The role of medications. Clin Res Cardiol. 2018;107:214-221

6. Núñez J, Bayés-Genís A, Zannad F, Rossignol P, Núñez E, Bodí V, Miñana G, Santas E, Chorro FJ, Mollar A, Carratalá A, Navarro J, Górriz JL, Lupón J, Husser O, Metra M, Sanchis J. Long-Term Potassium Monitoring and Dynamics in Heart Failure and Risk of Mortality.Circulation. 2018 Mar 27;137(13):1320-1330.