



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
Clinical outcomes in children with severe covid-19: a retrospective study in limited vs. enormous resource countries
Version: (Date: Day/Month/Year)
28/04/2021
Working Group Chair (name, ORCID ID, email, institution, country)
Eva Miranda Marwali, MD, PhD ORCID ID 0000-0002-0135-536x Email eva.marwali@pnhk.go.id ; evamarwali@yahoo.com Pediatric Cardiac ICU National Cardiovascular Center Harapan Kita, Jakarta, Indonesia
¹ Working group co-chair (name, ORCID ID, email, institution, country)
1. Hwa Jin Cho, MD, PhD ORCID ID 0000-0002-2458-8529 E mail chhj98@gmail.com Division of pediatric cardiology and pediatric intensive care, Department of Pediatrics, Chonnam National University Children's Hospital, Gwangju, South Korea 2. Dyah Kanya Wati, MD, PhD; ORCID ID 0000-0002-6633-7445 Email dyahkanyawati@unud.ac.id Faculty of Medicine, Universitas Udayana, Bali, Indonesia 3. Saptadi Yulianto, MD; ORCID ID 0000-0003-0824-2883 Email saptadiy@ub.ac.id Saiful Anwar Hospital, Malang, West Java, Indonesia

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)
<p>1. Ivy Cerelia Valerie, MD; ORCID ID 0000-0001-6361-1587 Email: lierrecv@gmail.com Negara General Hospital, Jembrana, Bali, Indonesia</p>
<p>2. Muhammad Rayhan, MD Email: rayhan_azrissal@yahoo.co.id National Cardiovascular Center Harapan Kita, Jakarta, Indonesia</p>
<p>3. Aria Kekalih, MD PhD; ORCID ID: 0000-0001-7811-097X Email: aria.kekalih@gmail.com Community Medicine Department, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia</p>

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

COVID-19 pandemic has occurred for one year, causing huge impact on health and socioeconomic conditions around the world. Severe Covid19 disease is widely reported in adults, but in children this disease is mostly reported to be milder than adults.^{1,2} In comparison to developed countries, only few reports have been made on the pediatric COVID-19 cases in developing countries. The latest report from a child referral hospital in Indonesia found that 20 out of 490 children (4%) who were confirmed or suspected of having Covid19 had died. The positivity rate for covid19 was also low, with only 50 confirmed positive cases of the 490 children tested (10.2%). All of these deceased children were confirmed Covid19, resulting in 40% death rate (20 out 50 children) among all pediatric patients with positive SARS-CoV-2 PCR. Further research on Covid19 in children is needed, especially in the group of severe and critically ill children.³ Evaluation of the clinical outcome of children with Covid19 who is critically ill and the risk factors that determine clinical outcomes are urgently needed for planning health services for children with Covid19.⁴⁻⁷ Research in developing countries with limited health facilities must be carried out immediately to assess the impact of the Covid19 problem in children and to increase preparedness for the next surge of Covid19 diseases. 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 February 2021, there are 33 countries contributing paediatric data.

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	
<p>A. This research is intended to evaluate the incidence of mortality and morbidities (MOF, Septic Shock, ARDS, AKI, DIC, Neurologic complication⁸, MIS-C^{9,10}), Total oxygen supply, Intubation time, PICU LOS, and Hospital LOS in children with severe COVID-19 cases reported in the ISARIC registry.</p> <p>B. Compare the incidence of mortality and morbidities, Intubation time, PICU LOS and Hospital LOS in children with severe COVID-19 cases from developed and developing countries data in ISARIC and ECMOCARD registry.</p> <p>C. Evaluate the Risk Factors for mortality and morbidities including:</p> <ul style="list-style-type: none"> a. Demographic factors: age, gestational age, weight, height, BMI, nutritional status (WHO standard), sex, ethnicity, immunization status (BCG, DPT, Pneumococcus. HIB, Measles, MMR), prematurity. b. COVID-19 examination results: Confirmed OR Negative OR not available but with clinically suspected. c. Comorbidities: <ul style="list-style-type: none"> ● Acquired chronic diseases: Chronic Lung Disease, Asthma, Cancer, Renal Disease, Liver Diseases, Hematologic Diseases, Other Viral or Bacterial Co-infection (Tuberculosis, Dengue, HIV, Malaria, Influenzae) ● Congenital disease: Congenital Heart Disease¹¹, Syndromes d. First Clinical presentation during Hospital/ PICU admission: clinical symptom such as fever, cough, dyspnea, diarrhea, nausea, cephalgia, anosmia, rash; PRISM score, Oxygen saturation index, Oxygen Index, Inotropic Score. Duration of symptoms prior to hospital admission and ICU admission. e. Laboratory results: Lowest, Highest and Mean/Median Hb, Ht, Leucocytes, CRP, Procalcitonin, Ferritin level, Lactate, Troponine T, CK-CKMB¹⁰, Coagulation function (Platelet, PT, APTT, Fibrinogen, D Dimer), organ function (Urea, Creatinine, ALT, AST, Albumin) f. Treatments: type of support and medication; length of treatment <ul style="list-style-type: none"> ● Nasal Cannula ● High Flow Nasal Cannula ● NIV ● Mechanical Ventilation: conventional, HFO, NO ● Prone position ● ECMO ● Steroids ● Antivirals: remdesivir, etc g. Infrastructures: 	

<ul style="list-style-type: none"> • Availability of ICU bed • Availability of oxygen resource • Type of hospital or medical facility (referral or non-referral hospital) <p>D. Compare the risk factors identified for mortality and morbidities between data from developed and developing countries.</p>
Proposed Target Population
<p>The target population comprises of children aged <19 years who are admitted to hospital with confirmed or suspected severe/critical ill COVID-19 and are recorded in the ISARIC database.</p> <p>Definition for COVID-19 grade of severity based on WHO classification.¹²</p>
Clinical Questions/Descriptive Analyses
<ol style="list-style-type: none"> 1. What is the incidence of mortality and morbidity (MOF, Septic Shock, ARDS, AKI, DIC, Neurologic complication, MIS-C), Intubation time, PICU LOS, and Hospital LOS in children with severe COVID-19? 2. What is the difference between developing and developed countries data of children with severe COVID-19 in terms of mortality and morbidity (MOF, Septic Shock, ARDS, AKI, DIC, Neurologic complication, MIS-C), Intubation time, PICU LOS, and Hospital LOS? 3. What are the risk factors of mortality and morbidity? Risk factors included in analysis are demographic and baseline clinical characteristics, COVID-19 examination results, Comorbidities, Laboratory results, Treatments and Infrastructures? 4. What is the difference between developing and developed countries data of children with severe COVID-19 in terms of risk factors of mortality and morbidities?
Planned Statistical Analyses, Methodology and Representation
<ol style="list-style-type: none"> 1. Demographic and baseline clinical characteristics presented in suitable data distribution 2. Clinical pattern frequency in bar plot 3. Clinical score and key biomarkers presented in suitable data distribution 4. Pathogen co-detection in nasopharyngeal secretion presented in suitable data distribution with narrative 5. Therapeutic measures (specific, supportive) presented in suitable data distribution 6. Survival analysis of mortality 7. Bivariate and multivariate analyses of independent variables with regard to the outcomes
Handling of Missing Data
<p>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 perform on them. Type of missingness shall be considered including whether data are not missing at</p>

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

Provide details of the timelines for dissemination of research findings.

May 2, 2021: Statistical Analysis Plan (SAP) submission to ISARIC

May – June 2021: Approval of SAP from ISARIC Committees and admitting input from ISARIC investigators

June – July 2021: Evaluate validity of data and Data analysis

July - August 2021: Results and Write manuscript

September 2021: Manuscript submission to the journal

References

1. Sinaei R, Pezeshki S, Parvaresh S, Sinaei R. Why COVID-19 is less frequent and severe in children: a narrative review. *World J Pediatr.* 2020; 17(1):10-20.
2. Williams PCM, Howard-Jones AR, Hsu P, Palasanthiran P, Gray PE, et al. SARS-CoV-2 in children: spectrum of disease, transmission and immunopathological underpinnings. *Pathology.* 2020 Dec;52(7):801-808
3. Dewi R, Kaswandani N, Karyanti MR, Setyant DB, Pudjiadi AH, Hendarto A, Djer MM, Prayitno A, Yuniar I, Indawati W, Prawira Y, Handryastuti S, Sjakti HA, Hidayati EL, Muktiarti D, Soebadi A, Puspaningtyas NW, Muhaimin R, Rahmadhany A, Octavius GS, Puspitasari HA, Jasin MR, Tartila T, Putri ND. Mortality in children with COVID-19: Lessons learned from a tertiary referral hospital in Indonesia. *Int J Infect Dis.* 2021 Apr; 12:S1201-9712(21)00330-1.
4. Mehta NS, Mytton OT, Mullins EWS, Fowler TA, Falconer CL, Murphy OB, Langenberg C, Jayatunga WJP, Eddy DH, Nguyen-Van-Tam JS. SARS-CoV-2 (COVID-19): What Do We Know About Children? A Systematic Review. *Clin Infect Dis.* 2020 Dec 3;71(9):2469-2479.
5. Williams N, Radia T, Harman K, Agrawal P, Cook J, Gupta A. COVID-19 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review of critically unwell children and the association with underlying comorbidities. *Eur J Pediatr.* 2021; 180:689–697
6. Xiaojian C, Zhao Z, Zhang T, Guo W, Guo W, et al. A systematic review and meta-analysis of children with Coronavirus Disease 2019 (COVID-19). *J Med Virol.* 2021 Feb;93(2):1057-1069.
7. Cui X, Zhang T, Zheng J, Zhang J, Si P, et al. Children with coronavirus disease 2019: A review of demographic, clinical, laboratory, and imaging features in pediatric patients. *J Med Virol.* 2020;1–10.
8. Lin JE, Asfour A, Sewell TB, Hooe B, Pryce P, et al. Neurological issues in children with COVID-19. *Neurosci Lett.* 2021 Jan 19;743:135567

9. Riollano-Cruz M, Akkoyun E, Briceno-Brito E, Kowalsky S, Posada R, et al. [OBJ] Multisystem Inflammatory Syndrome in Children (MIS-C) Related to COVID-19: A New York City Experience. *Med Virol*. 2021;93(1):424-433
10. Clinical management of COVID-19: interim guidance, 27 May 2020. World Health Organization. Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. *Eur J Pediatr*. 2021; 180:307–322.
11. Das BB. COVID-19 and Pulmonary Hypertension in Children: What Do We Know So Far? *Medicina (Kaunas)*. 2020 Dec 19;56(12):716.
12. World Health Organization. Clinical Management of COVID-19 interim guidance. 27 May 2020. <https://apps.who.int/iris/handle/10665/332196>