Short-term complications and post-acute sequelae in hospitalized pediatric patients with COVID-19 and obesity: a multicenter cohort study

Gonzalo Valenzuela[1,2], Gonzalo Alarcón-Andrade[1]; Clara Schulze-Schiapacasse[1]; Rocío Rodríguez[3]; Tamara García-Salum[1,2]; Catalina Pardo-Roa[1,2]; Jorge Levican[1]; Eileen Serrano[1], María José Avendaño[1]; Monserrat Gutiérrez[4,5], Loreto Godoy[4,5]; Pamela Céspedes[5]; Sandra Bermudez[5]; Javiera Aravena[4,6]; Irini Nicolaides[4,6]; Eliana Martínez[4]; Constanza Gómez-Canobbio[4]; Macarena Jofré[4];Andrea Salinas[4]; Daniela Depaoli[6]; Carolina Loza[4,6]; Andrés Muñoz[4,6]; Natalia Ormazábal[6]; Diana Manzur[3]; José Barriga[3]; Leonardo I. Almonacid[1]; Estefany Poblete-Cárdenas[1]; Erick Salinas[1,2]; Andrés Muñoz-Marcos[1]; Salesa Barja[4,7,8] and Rafael A. Medina[1,2,9].

Affiliations:

1 Department of Pediatric Infectious Diseases and Immunology, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile.
2 Advanced Interdisciplinary Rehabilitation Register (AIRR) – COVID-19 Working Group, Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile.
3 Hospital Clínico Red Salud UC-Christus, Santiago, Chile.
4 Department of Pediatrics, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile.
5 Hospital Dr. Sótero del Río, Santiago, Chile.
6 Hospital Clínico La Florida, Santiago, Chile.
7 Department of Pediatric Gastroenterology and Nutrition. School of Medicine. Pontificia Universidad Católica de Chile. Santiago, Chile.
8 Hospital Josefina Martínez, Santiago, Chile.
9 Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

Keywords: COVID-19; obesity; child; adolescent; intensive care units; post-acute COVID-19 syndrome

Running title: COVID-19 complications in children with obesity

Address correspondence to: Rafael A. Medina, Department of Pediatric Infectious Diseases and Immunology, Marcoleta, Santiago, Chile, 391. E-mail: rmedinai@uc.cl.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5,7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-11
		(*b*) Report category boundaries when continuous variables were categorized	8, 16, 18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

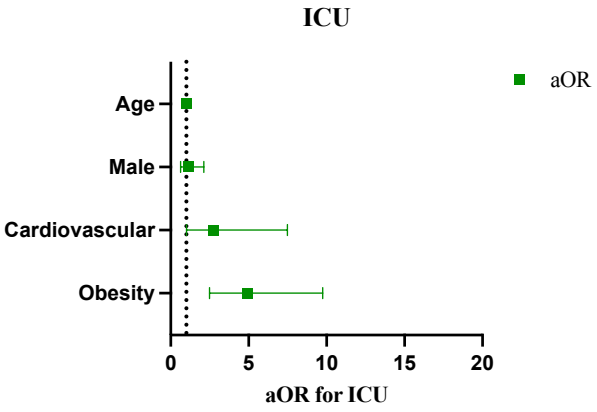
Supplemental file 2. Vital signs and laboratory findings at admission of inpatients infected with SARS-CoV-2 according to the presence of obesity.

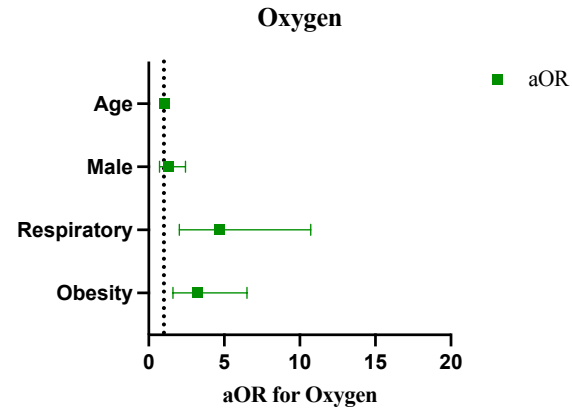
Variables	All patients (n=216)†	Patients with obesity (n=67)†	Patients without obesity (n=149)†	P value
Vital signs*:				
Temperature (°C), median (IQR)	37.3 (36.4-38.3)	37.0 (36.4-38.3)	37.5 (36.5-38.3)	0.486
Temperature ≥38°C, n (%)	76 (35.19)	24 (35.82)	52 (34.90)	0.896
Tachycardia, n (%)	106 (49.07)	49 (73.13)	57 (38.26)	**<0.001**
Tachypnea, n (%)	116 (53.70)	52 (77.61)	64 (42.95)	**<0.001**
SpO2, n (%)	96 (93-98)	95 (90-98)	97 (94-98)	0.053
Laboratory parameter				
Complete blood count** (n=214)				
Anemia, n (%)	41 (19.16)	8 (12.2)	33 (22.30)	0.081
Leucopenia, n (%)	52 (24.30)	15 (22.73)	37 (25.00)	0.720
Leukocytosis, n (%)	39 (18.22)	10 (15.15)	29 (19.59)	0.437
Neutropenia, n (%)	22 (10.28)	4 (6.06)	18 (12.16)	0.175
Neutrophilia, n (%)	49 (22.90)	15 (22.73)	34 (22.97)	0.968
Lymphopenia, n (%)	97 (45.33)	36 (54.55)	61 (41.22)	0.070
Lymphocytosis, n (%)	7 (3.27)	0 (0)	7 (4.73)	NA
Thrombocytopenia, n (%)	31 (14.49)	11 (16.67)	20 (13.51)	0.545
Thrombocytosis, n (%)	45 (21.03)	8 (12.12)	37 (25.00)	**0.033**
C-Reactive Protein ** (n=206)				
C-Reactive Protein (mg/dL), median (IQR)	1.38 (0.24-8.39)	3.02 (1.00-12.58)	0.71 (0.15-6.07)	**<0.001**
C-Reactive Protein ≥3 mg/dL, n (%)	82 (39.81)	33 (50.00)	49 (35.00)	**0.040**

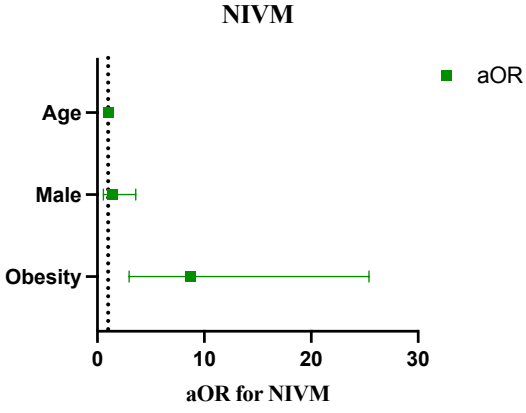
Univariate analyses were performed accordingly with chi-square, Fisher's exact and Mann-Whitney-

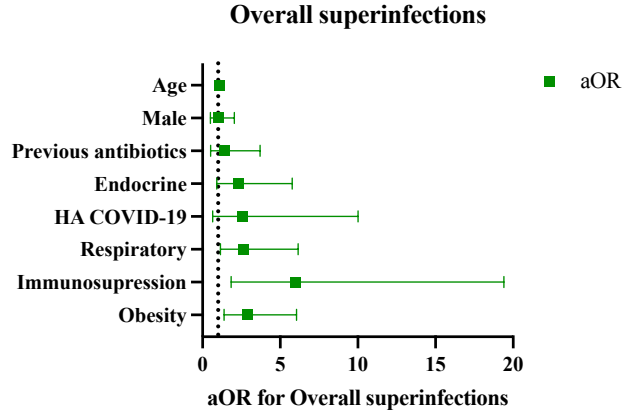
Wilcoxon tests. Statistical significance was set at p value <0.05. IQR: Interquartile range; NA: Not Applicable. †214 patients had a complete blood count (66 with obesity and 148 without obesity), and 206 patients had C-reactive protein results (66 with obesity and 140 without obesity). *Vital signs were interpreted according to age following the Pediatric Advanced Life Support (PALS) guidelines. **Blood cell counts were interpreted following age reference intervals determined by Lubin et al 1994.

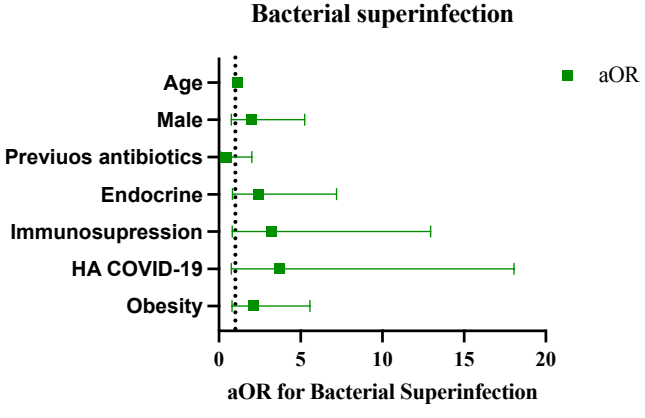
Supplemental file 3. Adjusted odds ratios for short-term complications in pediatric patients with obesity and COVID-19. Covariables used to adjust models for each outcome are detailed in each graph. Abbreviations: OR: Odds Ratio, ICU: Intensive Care Unit, NIMV: Noninvasive Mechanical Ventilation, HA COVID-19: Healthcare-Associated COVID-19.

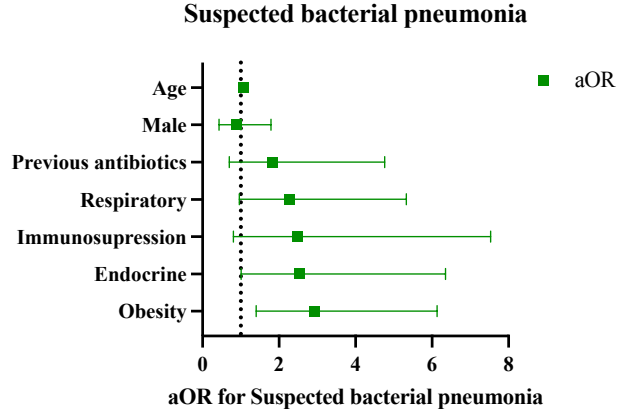

ICU
aOR
Age
Male
Cardiovascular
Obesity
0
5
10
15
20
aOR for ICU


Oxygen
aOR
Age
Male
Respiratory
Obesity
0
5
10
15
20
aOR for Oxygen

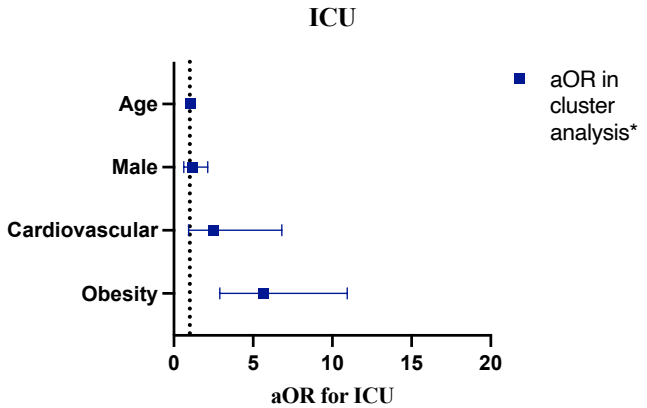

NIVM
aOR
Age
Male
Obesity
0
10
20
30
aOR for NIVM

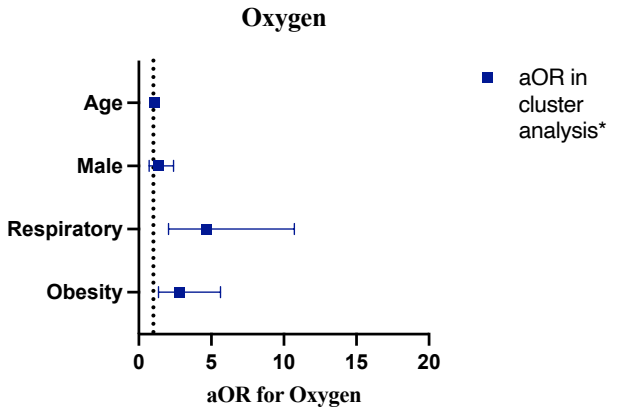

Overall superinfections
aOR
Age
Male
Previous antibiotics
Endocrine
HA COVID-19
Respiratory
Immunosupression
Obesity
0
5
10
15
20
aOR for Overall superinfections

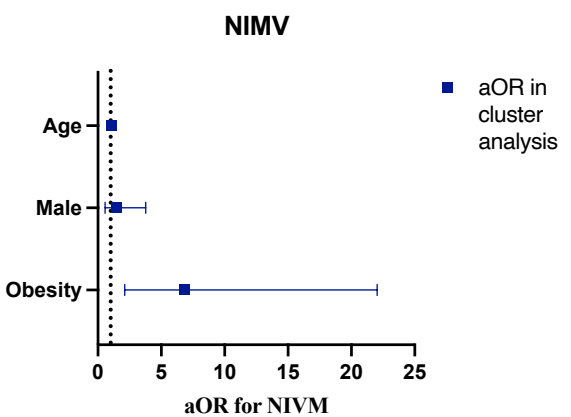

Bacterial superinfection
aOR
Age
Male
Previuos antibiotics
Endocrine
Immunosupression
HA COVID-19
Obesity
0
5
10
15
20
aOR for Bacterial Superinfection

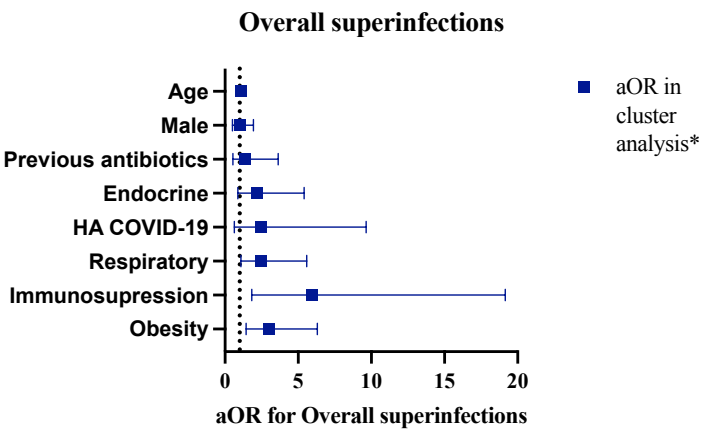

Suspected bacterial pneumonia
aOR
Age
Male
Previous antibiotics
Respiratory
Immunosupression
Endocrine
Obesity
0
2
4
6
8
aOR for Suspected bacterial pneumonia

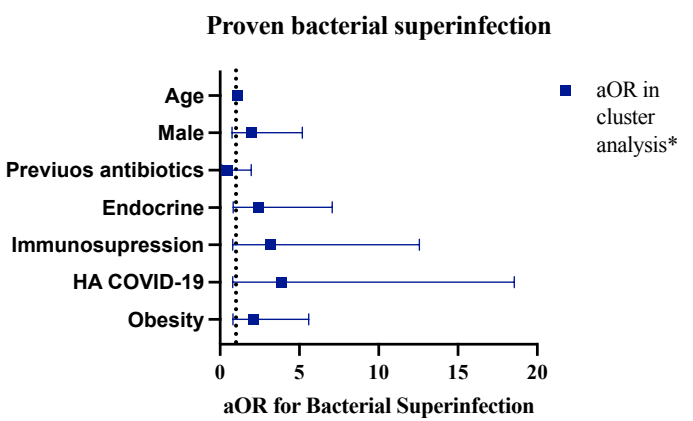
Supplemental file 4. Adjusted odds ratios in cluster analysis for short-term complications in pediatric patients with obesity and COVID-19. Cluster analysis is based on dependency given by the hospital at admission and the time period of the predominant lineage or variant of concern. Covariables use to adjust models for each outcome are detailed in each graph. Abbreviations: OR: Odds Ratio, ICU: Intensive Care Unit, NIMV: Non-Invasive Mechanical Ventilation, HA COVID-19: Healthcare-Associated COVID-19.

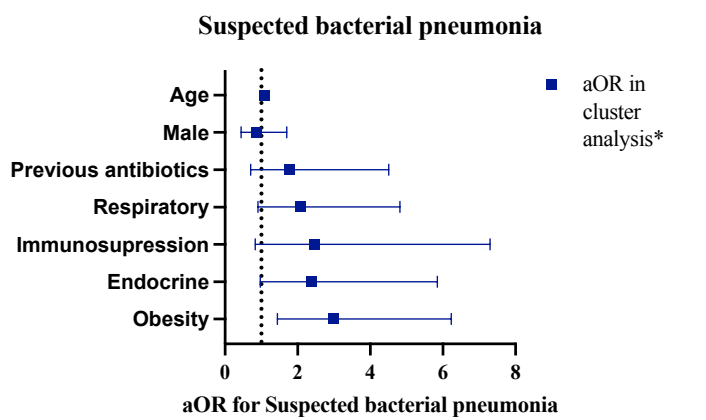

ICU
Age
Male
Cardiovascular
Obesity
0
5
10
15
20
aOR for ICU
aOR in cluster analysis*


Oxygen
Age
Male
Respiratory
Obesity
0
5
10
15
20
aOR for Oxygen
aOR in cluster analysis*


NIMV
Age
Male
Obesity
0
5
10
15
20
25
aOR for NIVM
aOR in cluster analysis


Overall superinfections
Age
Male
Previous antibiotics
Endocrine
HA COVID-19
Respiratory
Immunosupression
Obesity
0
5
10
15
20
aOR for Overall superinfections
aOR in cluster analysis*


Proven bacterial superinfection
Age
Male
Previuos antibiotics
Endocrine
Immunosupression
HA COVID-19
Obesity
0
5
10
15
20
aOR for Bacterial Superinfection
aOR in cluster analysis*


Suspected bacterial pneumonia
Age
Male
Previous antibiotics
Respiratory
Immunosupression
Endocrine
Obesity
0
2
4
6
8
aOR for Suspected bacterial pneumonia
aOR in cluster analysis*

Supplemental file 5. Age-adjusted versus age-stratified analysis of the main outcomes.

Variable	**Age-adjusted aOR (CI95%) n=216**	**Age-stratified analysis**	
		aOR for patients 12 years and over (CI95%) n=88	**aOR for patients under 12 years (CI95%) n=128**
ICU admission	5.63 (2.90-10.94)*	9.61 (4.21-21.94)*	3.60 (1.47-8.83)*
Oxygen	2.77 (1.36-5.63)*	5.60 (2.05-15.34)*	2.24 (0.83-6.03)
NIMV	6.81 (2.11-22.04)*	17.09 (1.78-163.82)*	2.51 (0.44-14.41)
Overall superinfections	3.02 (1.45-6.31)*	1.49 (0.56-3.93)	7.21 (2.30-22.63)*
Suspected bacterial pneumonia	3.00 (1.44-6.23)*	2.09 (0.78-5.56)	6.69 (2.20-20.38)*
Dyspnea	9.91 (1.92-51.10)*	6.38 (0.71-57.91)	16.52 (1.67-164.66)*
Muscle weakness	20.04 (2.50-160.65)*	10.34 (1.22-87.41)*	NA#

Analysis performed following generalized estimating equations methodology (cluster analysis).

* Statistically significant ($p<0.05$).

All patients under 12 years old with muscle weakness at follow-up had obesity.

ICU: intensive care unit; NIMV: non-invasive mechanical ventilation; aOR: adjusted odds ratio; CI95%: 95% confidence interval.