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ORIGINAL ARTICLE

Experience in COVID-19 in hospitalized patients in pediatric critical units during pandemic period

Experiencia en COVID-19 en pacientes hospitalizados en unidades de paciente crítico pediátrico durante el periodo pandémico

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What do we know about the subject matter of this study?

SARS-CoV-2, responsible for the largest pandemic in the last century, initially appeared to have a more benign course in the pediatric population. However, it is now known that children can also develop severe symptoms, especially the so-called multisystem inflammatory syndrome in children by SARS-CoV-2.

What does this study contribute to what is already known?

This multicenter study describes the behavior of COVID-19 in Chilean children hospitalized in critical care units during the pandemic (2020-2021), to evaluate those risk factors associated with the development of a severe clinical picture caused by SARS-CoV-2 in our pediatric population.

Abstract

Objectives: To characterize the COVID-19 disease profile in Chilean children hospitalized in pediatric intensive care units (PICU) and to evaluate risk factors associated with severe COVID-19. **Patients and Method:** A multicenter prospective cohort study with patients 0-18 years of age with confirmed SARS-CoV-2 hospitalized in PICU. Clinical, laboratory, imaging, and therapeutic variables were recorded. We compared "mild/moderate COVID-19" with "severe COVID-19" using median with interquartile range (IQR), Mann-Whitney U test, two-tailed Fisher's test, and forward binary multivariate analysis to adjust variables for "severe COVID-19". A $p < 0.05$ was considered significant. **Results:** From 16 PICUs, 219 patients were recruited, 55.3% were male, with a median age of 86 months (IQR: 13.5-156). The most frequent comorbidities were obesity and respiratory diseases. Overall mortality was 3.6%. "Severe COVID-19" (26.5%) showed more leukopenia, lymphopenia, increased inflammatory parameters, and altered organ function ($p < 0.05$). It also developed more sepsis/shock, ARDS, and organ dysfunction, requiring more hemodynamic, anti-inflammatory, anticoagulation, and antibiotic therapy, with a longer stay in the PICU/hospital ($p < 0.05$), and 13.8% of mortality. Risk factors associated with "severe COVID-19" were shock on admission to the PICU [aOR 28.44 (95%CI 10.45-77.4)], obesity [aOR 3.55 (95%CI 1.3-9.6)], consolidation [aOR 3.1 (95%CI 1.1 -8.7)], atelectasis [aOR: 8.7 (95%CI 1.17-64.3)], stress dose of corticosteroids [aOR 7.7 (95%CI 1.9-30.6)], early antibiotic therapy [aOR: 12.02 (95%CI 1.11-130.02)], acquired/congenital immunodeficiency [aOR: 19.2 (95%CI: 1.19-321)], and oncological pathology [aOR 10.7 (95%CI 2.14-47.8)]. **Conclusion:** In this Chilean pediatric cohort, most patients with COVID-19 admitted to de PICU were male, of school age, with associated comorbidity. Risk factors for developing severe COVID-19 were the presence of comorbidities such as acquired/congenital immunodeficiency, oncological pathology, and obesity, in addition to shock on admission and consolidations on X-rays.

Keywords:
Children;
SARS-CoV-2;
COVID-19;
Critical Care;
Severe COVID-19

Introduction

SARS-CoV-2 is a betacoronavirus, belonging to the coronaviridae family, like SARS-CoV-1 and MERS-CoV. Described in December 2019 in the context of an outbreak of pneumonia with atypical evolution in Wuhan City, Hubei province, China, probably secondary to zoonosis. Its transmission mechanism occurs via respiratory droplets, fomites, and the fecal-oral route[1-3]. Transmission of the virus can occur from both symptomatic and asymptomatic patients, as similar viral loads have been demonstrated in both groups[4,5].

Given its rapid spread, in March 2020, the World Health Organization (WHO) declared the spectrum of clinical syndromes produced by the SARS-CoV-2 virus a pandemic, encompassed under the term COVID-19 (*coronavirus infectious disease-19*)[6]. SARS-CoV-2 infection varies from mild symptoms to acute respiratory distress syndrome (ARDS), shock, organ dysfunction, and death[7,8]. It mainly affects the adult population, without gender predominance, with a mortality rate between 2.4 to 5%. It has a greater severity and mortality in older patients with comorbidities such as diabetes, hypertension, obesity, and chronic pulmonary and cardiovascular diseases, reaching mortality figures close to 50% in this susceptible group[2,8].

Multiple studies have been published on the epidemiology, clinical course, and management of COVID-19 in adults. In the pediatric population, the frequency of COVID-19 ranges from 1.2 to 5%, usually secondary to intrafamilial transmission, with a milder clinical course compared with adults, and similar symptoms (fever, cough, odynophagia, myalgia, vomiting, diarrhea), although many of them present asymptomatic[1,9-11]. Less than 1% of affected children would require hospitalization, with the most severe cases being associated with younger age and the presence of some comorbidities[9,10,12]. In this context, this study aims to characterize the behavior of COVID-19 in Chilean children hospitalized in pediatric intensive critical

units (PICU) during the pandemic and to evaluate the risk factors associated with a severe clinical course of COVID-19.

Patients and Method

Prospective multicenter cohort study between April 2020 and August 2021. Patients between 0 and 18 years old with a laboratory-confirmed diagnosis of SARS-CoV-2 [polymerase chain reaction (PCR) or IgG and/or IgM serology] hospitalized in a public or private PICU in our country were enrolled.

The recording of the enrolled patients' data was carried out by a designated physician from each participating center, using a digital form restricted to the responsible investigators. The clinical variables registered in the digital form were sex, age, admission severity score (PIM-2), hospital and PICU length-of-stay, admission diagnosis, comorbidities, type of infection, the time between symptom onset and hospitalization, clinical disease presentation and evolution, availability of images, and their description [chest X-ray and/or computed axial tomography (CT)], coinfection status and microorganism identified if it was clinically relevant for the responsible investigator, laboratory tests [hematocrit, hemoglobin, leukocytes, lymphocytes, platelets, blood creatinine, liver enzymes, C-reactive protein, procalcitonin (PCT), lactate dehydrogenase (LDH), INR, D-dimer, troponin], ventilatory support [oxygen therapy, high-flow nasal cannula (HFNC), and noninvasive mechanical ventilation (NIMV), invasive mechanical ventilation (IMV)]. The prescription of the following therapies aimed at specific management of COVID-19: empirical drugs (hydroxychloroquine, azithromycin, lopinavir/ritonavir, remdesivir, oseltamivir), anti-inflammatory drugs (hydrocortisone, methylprednisolone, dexamethasone, intravenous immunoglobulins, tocilizumab), and anticoagulant therapy. In addition, the use of bronchodilators, antimicrobials, and vasoactive drugs was recorded. Complications and patient outcomes in the PICU (alive, deceased) were also recorded.

Considering COVID-19 an emerging entity with uncertain evolution, many children with confirmed SARS-CoV-2 were admitted to PICU at the beginning of the pandemic for monitoring, independent of their clinical condition. Thus, one of the database diagnostic codes for this feature was "Caution/Observation". Likewise, patients admitted to PICU for a cause other than COVID-19 in whom screening for SARS-CoV-2 was positive were categorized in the diagnostic item as "Other". Data for all patients were anonymized. Participating units were blinded to patient information recorded by other centers. Access to general information and the database was restricted to the study's principal investigators using a unique, nontransferable password.

Two groups were defined to assess risk factors for developing severe COVID-19: those with "mild/moderate COVID-19" and those with "severe COVID-19". The group of patients with "severe COVID-19" was defined by the need for IMV associated with the requirement of vasoactive drugs and/or rescue ventilatory therapies (prone position, continuous neuromuscular blockade, inhaled nitric oxide (iNO), high-frequency oscillatory ventilation (HFOV), and/or requirement of extracorporeal therapies (Hemofiltration, Plasmapheresis, ECMO).

The project was approved by the Scientific Ethics Committee of each participating center, with the waiver of informed consent, as it was an observational, descriptive study, without interventions for the patients. This study was carried out under the ethical principles of the Declaration of Helsinki.

Statistical analysis

The median and interquartile range (IQR) were used to describe the numerical variables. The Mann-Whitney U test was used for numerical variables and the two-tailed Fisher test for categorical variables. For the management of confounding variables, a forward binary multivariate analysis was performed to adjust the following variables according to previous reports: sex, comorbidities, age < 6 months, oncologic pathology, obesity, immunodeficiency, chronic lung disease, chest retraction on physical examination, dyspnea, pneumonia or atelectasis on chest X-ray or thorax CT, use of antibiotics, corticosteroids in stress doses, coinfection, and shock at admission, for the outcome defined as "severe COVID-19"[13-18]. Odds ratio (OR) values are presented for both univariate and multivariate analyses with a 95% confidence interval. Statistical analysis was performed with SPSS V25.0 (NY, USA) software, and any p-value < 0.05 was considered significant.

Results

Overall results

Sixteen PICU, both public and private, participated in the study, with 219 patients registered during the period analyzed. Of the total number of patients, 121 were male with a median age of 86 months (IQR: 13.5-156 months) and a female:male ratio of 1:1.2. The main symptoms of the patients enrolled at the time of admission were fever, polypnea, cough, and vomiting. The least frequent symptoms were anosmia, arthralgia, stridor, and ageusia. Table 1 shows the characteristics

of the group of patients enrolled in this study and Figure 1 shows the symptomatology recorded in this cohort. Regarding the clinical evolution of the patients, it was observed that those with pneumonia developed ARDS in 33.3%, sepsis/shock in 16.7%, and organ dysfunction in 13.9%. In the group of patients with Kawasaki disease, 52% developed sepsis/shock, and 24% developed organ dysfunction, and, of the patients diagnosed with multisystem inflammatory syndrome in children (MIS-C), 100% developed sepsis/shock and organ dysfunction.

Patient analysis according to COVID-19 severity

The group of patients with mild/moderate COVID-19 corresponded to 161 (73.5%) and 58 with severe COVID-19 (26.5%). The latter group due to its severity presented shock/sepsis (n = 36), respiratory failure (n = 18), upper airway obstruction (n = 2), and altered state of consciousness (n = 2) (Tables 2 and 3). When comparing these two groups, no differences were observed in sex, age, comorbidity, type of contact, time of symptom onset and admission to PICU, presence of symptoms, and admission diagnoses, except for the diagnosis of "Other", where patients predominate in the mild/moderate COVID-19 group (Table 2).

The "severe COVID-19" group developed significantly more sepsis/shock, ARDS, and organ dysfunction, in addition to presenting more pneumonia, atelectasis, and ground glass patterns on radiological images. In this same group, more methylprednisolone, steroids in stress dose, intravenous immunoglobulin, heparin, antibiotics, vasoactive drugs, and red blood cell transfusion were used. The latter also had higher PIM-2 scores, high frequency of bacterial co-infection, longer PICU and total hospital LOS compared with the "mild/moderate COVID-19" group. The two groups had no differences in the non-invasive ventilatory support use.

When analyzing laboratory tests, the "severe COVID-19" group presented lower neutrophil, lymphocyte, and platelet counts, higher creatinine, AST/ASP transaminases, LDH, inflammatory parameters (CRP, PCT, ferritin), INR, D-dimer, troponin, and Pro-BNP compared with the "mild/moderate COVID-19" group (Table 4). In the "severe COVID-19" group, the rescue therapies recorded in severe respiratory failure were neuromuscular blockade in 42% (17/21 pneumonia), prone position 39.2% (16/20 pneumonia), iNO 12% (5/6 pneumonia), and HFOV 8% (3/4 pneumonia). No ECMO or hemofiltration was required in this group of patients. The clinical complications registered (Table 5) were all significant in the "severe COVID-19" group [except for disseminated intravascular coagulation (DIC)].

Deaths were observed only in the "severe CO-

Table 1. Characteristics of the cohort of COVID-19 hospitalized patients in PICU during the pandemic period (n = 219).

Characteristics	Patient number (%)
Gender	
Male	121 (55.3)
Female	98 (44.7)
Comorbidities	
Obesity	64 (29.2)
Respiratory*	29 (13.2)
Immunodeficiency	13 (5.9)
Preterm	10 (4.5)
Malnutrition	11 (5.0)
Diabetes	7 (3.1)
Congenital heart diseases	8 (3.6)
Other	61 (27.89)
SARS-CoV-2 detection	
Upper respiratory airway RT-PCR	162 (74.0)
Lower respiratory airway RT-PCR	5 (2.3)
Serology (Ig M y/o Ig G)	52 (23.7)
Transmission mechanism	
Household	120 (54.8)
Extra household	6 (2.7)
Healthcare setting	11 (5.0)
Unknown	82 (37.4)
Presence of symptoms at the time of diagnosis	
Yes	196 (89.5)
No	23 (10.5)
Admission Diagnosis	
Pneumonia	72 (32.9)
Kawasaki Diseases	25 (11.4)
PIMS	12 (5.5)
Myocarditis/Heart failure	10 (5.0)
Rhinopharyngitis	7 (3.2)
Observation/Precaution**	4 (1.8)
Encephalitis/Seizure	3 (1.4)
Pleuropneumonia	1 (0.5)
Bronchiolitis	1 (0.5)
Other***	84 (38.3)
Chest- X Ray Pattern	181 (82.6)
Normal	53 (29.3)
Interstitial pattern	69 (38.1)
Single consolidation	10 (5.5)
Multiple consolidation	34 (18.7)
Atelectasis	5 (2.7)
Pleural Effusion	5 (2.7)
Thorax CT	36 (16.4)
Clinical evolution	
Sepsis/Shock	71 (32.4)
ARDS	32 (14.6)
Multiorgan Failure	48 (21.9)
Mortality	8 (3.6)

RT-PCR: Reverse Transcription Polymerase Chain Reaction; PIMS: Pediatric Inflammatory Multisystem Syndrome; CT: Computed Tomography scan; ARDS: Acute Respiratory Distress Syndrome; PICU: Pediatric Intensive Care Unit. *Includes: asthma, bronchopulmonary dysplasia, chronic lung damage, bronchial hyperreactivity, cystic fibrosis. **Patients with confirmed SARS-CoV-2 were admitted to UPCP for monitoring. ***Patients admitted to UPCP for another diagnosis in whom SARS-CoV-2 was screened upon admission.

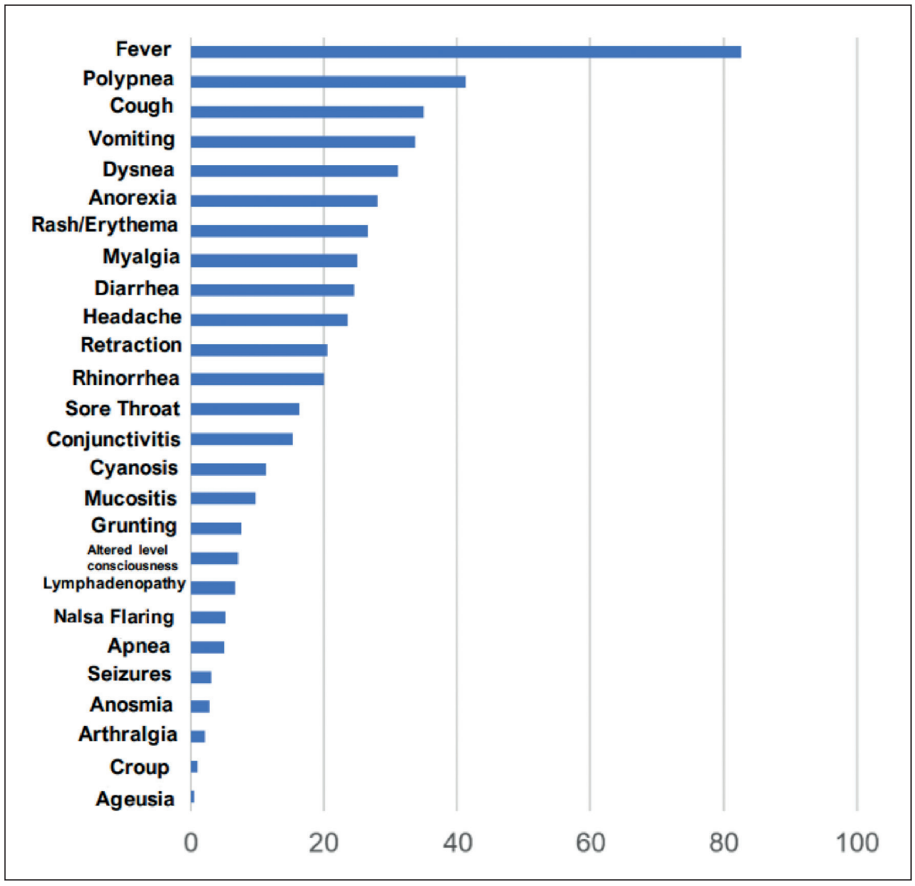

Figure 1. Symptoms and presentation signs by frequency, recorded in symptomatic SARS-CoV-2 patients admitted to the Pediatric Intensive Care Unit (PICU) (n=196).

VID-19" group with a 13.8% rate (Table 3). When evaluating the severe COVID-19 subgroup of patients according to death, the admission diagnoses were pneumonia (n = 3), shock (n = 2), encephalitis (n = 1), myocarditis (n = 1), and autoimmune lymphoproliferative syndrome (n = 1). Factors associated with mortality in the univariate analysis were primary or acquired immunodeficiency as comorbidity (OR: 49 [95% CI: 4.3-549]), presence of pneumonia on admission thorax CT (OR: 7. 3 [95% CI: 1.4-37.3]), stress-dose steroids (OR: 13.7 [95% CI: 2.4-79.1]), red blood cell and platelet transfusions, and fungal co-infection during PICU stay (Supplementary Table 1, available online version).

Finally, a forward binary logistic analysis was performed to determine those risk factors associated with severe COVID-19 in pediatrics and to adjust confounding cofactors[9,10,13-15,19]. Adjustment was made for sex, age < 6 months, comorbidities, oncologic pathology, obesity, immunodeficiency, asthma, chronic lung disease, chest retraction on physical examination, dyspnea, pneumonia or atelectasis on chest X-ray or Thorax CT, antibiotic use, corticosteroids in stress dose, coinfection, and shock on admission time. Risk factors associated with "severe COVID-19" were shock on admission to PICU (aOR: 28.44 [95% CI: 10.45-77.4]), obesity (aOR: 3.55 [95% CI: 1.3-9.6]), opacity in chest X-Ray (aOR: 3.1 [95% CI: 1.1-8.7]), atelectasis on chest Rx (aOR: 8.7 [95% CI: 1.17-64.3]), stress-dose corticosteroids on admission (aOR: 7.7 [95%CI: 1.9-30.6]), early antibiotic prescription (aOR: 12.02 [95%CI: 1.11-130.02]), acquired and congenital immunodeficiency (aOR: 19.2 [95% CI: 1.19-321]), and oncologic diseases (aOR: 10.7 [95% CI: 2.14-47.8]) (Figure 2).

Discussion

This study, initiated at the beginning of the pandemic, included 219 pediatric patients hospitalized in different PICUs in Chile for whom SARS-CoV-2 was confirmed. As reported, there was a predominance of male patients, concentrated in the school-age age range[11,16,17]. More than half of the patients had at least one associated comorbidity, with obesity and chronic respiratory diseases being the most frequent, in figures somewhat higher than those reported in the literature[11,15,16]. Intra-domiciliary contact of SARS-CoV-2

Table 2. Comparison between groups of pediatric critical patients with confirmed SARS-CoV-2 admitted to PICU according to the type of evolution (n = 219).

Clinical features	Mild/moderate (n = 161)	Severe (n = 58)	OR (IC 95%)	p Value
Male gender	93 (57.8)	28 (48.3)	0.68 (0.37-1.24)	0.22
Age, months. Median (IQR)	89 (13.5-157)	74.5 (12.5-153)		0.98
Comorbidities				
Obesity	43 (26.7)	21 (36.2)	1.5 (0.82-2.9)	0.18
Respiratory*	18 (11.2)	11 (18.9)	0.5 (0.23-1.2)	0.2
Immunodeficiency	8 (5.0)	5 (8.6)	1.8 (0.56-5.7)	0.33
Preterm	7 (4.3)	3 (5.2)	1.2 (0.3-4.8)	0.72
Malnutrition	6 (3.7)	5 (8.6)	2.4 (0.7-8.3)	0.17
Diabetes	4 (2.5)	3 (5.2)	0.4 (0.1-2.1)	0.54
Congenital Heart Diseases	4 (2.5)	4 (6.9)	2.9 (0.7-12.03)	0.21
Other	57 (35.4)	17 (29.3)	0.7 (0.39-1.45)	0.25
Contact type with a COVID-19 case				
Within Hospital	6 (3.7)	5 (8.6)		0.26
Known extra household	5 (3.1)	1 (1.7)		
Intradomicile	92 (57.1)	28 (48.3)		
Unknown	58 (36)	24 (41.4)		
Time between symptom onset and admission to PICU	4 (2-6)	4 (3-5)		0.7
Symptomatic patient	141 (87.6)	55 (94.8)	0.38 (0.11-1.3)	0.14
Admission diagnosis				
Pneumonia	51 (31.7)	21 (13)	0.8 (0.4-1.5)	0.63
Kawasaki disease	15 (9.3)	10 (17.2)	0.4 (0.2-1.17)	0.1
PIMS	7 (4.3)	5 (8.6)	0.48 (0.14-1.5)	0.2
Myocarditis/Heart failure	6 (3.7)	4 (6.9)	0.52 (0.14-1.9)	0.51
Rhinopharyngitis	5 (3.1)	2 (3.4)	0.8 (0.16-4.7)	1.0
Observation/Precaution**	4 (2.5)	0 (0)		
Encephalitis/Seizure	2 (1.2)	1 (1.7)	0.7 (0.06-8.0)	1.0
Pleuropneumonia	1 (0.6)	0 (0)		
Bronchiolitis	1 (0.6)	0 (0)		
Other***	69 (42.9)	15 (25.9)	2.1 (1.1-4.1)	0.003#

#Significant. Abbreviations: IQR: Interquartile Range; PIMS: Pediatric Inflammatory Multisystem Syndrome; CI: Confidence Interval; OR: odds ratio; PICU: Pediatric Intensive Care Unit; IQR: Interquartile range. Includes: asthma, bronchopulmonary dysplasia, chronic lung damage, bronchial hyperreactivity, cystic fibrosis. ** Patients with confirmed SARS-CoV-2 admitted to UPCP for monitoring. ***Patients admitted to UPCP for another diagnosis in whom SARS-CoV-2 was screened upon admission

occurred in 55% of the patients, similar to rates reported in other studies (35 to 80%)[11,20,21]. In 11 patients (5.0%), the infection was nosocomial and corresponded to children with chronic pathologies, with prolonged hospital stays, both risk factors described for in-hospital infection[22].

Although most of the patients admitted to PICU were symptomatic for COVID-19, 10.5% of them were found to have SARS-CoV-2 because of the protocolized active search for this virus in children admitted due to another cause[23]. In symptomatic patients, as in other reports, the most frequent clinical manifestation was fever followed by respiratory and gastrointestinal symptoms, with ageusia and anosmia being very infrequent, probably due to the difficulty children have in expressing this type of symptomatology[10,15,19-21,23]. The diagnoses of admission to the PICU were varied, ranging from hospitalization for observation to pathologies related or not to COVID-19 ("Other" category). Within the categories related to COVID-19, pneumonia was the main diagnosis in one-third of the patients, followed by Kawasaki disease in 11.4%, and MIS-C in 5.5%. Of all patients, one-third developed sepsis/shock, one-fifth organ dysfunction, and 15% ARDS; all pathologies and evolutions were described in patients with COVID-19 in different published series.

In the group of patients with Kawasaki disease and MIS-C, the evolution to sepsis/shock was the most fre-

Table 3. Clinical, radiological, and management of pediatric critical patients with confirmed SARS-CoV-2 admitted to PICU according to the type of evolution (n = 219)

Clinical features	Mild/moderate	Severe	OR (CI 95%)	p Value
Sepsis/Shock	27 (16.8)	43 (74.1)	14.2 (6.9-29.2)	< 0.001*
ARDS	7 (4.3)	25 (43.1)	16.7 (6.7-41.7)	< 0.001*
Multiorgan Failure	25 (15.6)	22 (37.9)	3.3 (1.6-6.5)	0.001*
Radiological Diagnosis				
Atelectasis	4 (2.5)	4 (6.9)	2.9 (0.7-12.03)	0.21
Pleural effusion	3 (1.9)	2 (3.4)	1.9 (0.3-11.6)	0.6
Pneumonia	28 (17.4)	19 (32.8)	2.3 (1.2-4.6)	0.02*
Thorax CT diagnosis				
Atelectasis	2 (1.2)	4 (6.9)	5.9 (1.04-33.1)	0.04*
Pneumonia	11 (6.8)	10 (17.2)	2.8 (1.13-7.1)	0.03*
Pleural Effusion	2 (1.2)	2 (3.4)	2.8 (0.4-20.6)	0.28
Pneumothorax	0 (0)	2 (3.4)		
Ground-glass opacities	9 (5.6)	9 (15.5)	3.1 (1.2-8.3)	0.03*
COVID-19 empirical treatment				
Hydroxychloroquine	5 (3.8)	1 (1.9)	0.5 (0.1-4.2)	0.67
Azithromycin	13 (10)	6 (11.5)	1.17 (0.4-3.3)	0.8
Ivermectin	0 (0)	0 (0)		
Lopinavir/ritonavir	0 (0)	0 (0)		
Remdesivir	0 (0)	0 (0)		
Oseltamivir	1 (0.8)	0 (0)		
Tocilizumab	0 (0)	0 (0)		
Systemic corticosteroids				
Hydrocortisone	4 (3.1)	4 (8.3)	2.9 (0.7-12.03)	0.21
Methylprednisolone	35 (25.4)	32 (58.2)	4.1 (2.11-7.9)	< 0.001*
Dexamethasone	37 (28)	19 (37.3)	1.5 (0.77-3.01)	0.28
Stress-dose steroids	5 (3.1)	15 (25.9)	10.9 (3.7-31.6)	< 0.001*
IVIG	37 (27.4)	33 (60)	3.9 (2.1-7.7)	< 0.001*
Heparin	53 (38.7)	44 (78.6)	5.8 (2.8-12)	< 0.001*
Antibiotics prescription	109 (67.7)	57 (98.3)	27.2 (3.7-201.8)	< 0.001*
Bronchodilators	16 (9.9)	11 (19)	2.1 (0.9-4.8)	0.1
Vasoactive drugs	10 (6.2)	46 (79.3)	57.9 (23.5-142.6)	< 0.001*
Plasmapheresis	0 (0)	1 (2)		
Blood-derived product Transfusion				
Red Blood Cells	8 (6.1)	20 (36.4)	8.7 (3.6-21.6)	< 0.001*
Fresh frozen plasma	1 (0.8)	1 (2.0)	2.6 (0.16-42)	0.49
Cryoprecipitate	0 (0)	0 (0)		
Platelets	2 (1.5)	4 (7.7)	5.3 (0.94-30.1)	0.057
Coinfection				
Bacterial	21 (13)	16 (27.6)	2.5 (1.2-5.3)	0.015*
Viral	2 (1.2)	2 (3.4)	2.8 (0.39-20.6)	0.28
Fungal	0 (0)	7 (12.1)		
PICU LOS, median (IQR), days	3 (2-5)	9 (5-17.3)		< 0.001*
Hospital LOS, median (IQR), days	6 (3-9)	13.5 (7-24)		< 0.001*
PIM-2	1.4 (0.8-2.8)	3.2 (1.18-7.1)		< 0.001*
HFNC	12 (9.1)	3 (6)**	0.63 (0.17-2.4)	0.76
CPAP	1 (0.8)	2 (3.9)**	5.3 (0.47-59.4)	0.19
NIVM BiPAP	33 (25)	20 (37)**	1.8 (0.9-3.5)	0.11
Mortality	0	8 (13.8%)		

*Significant. **Patients who failed non-invasive support and required intubation and mechanical ventilation. Abbreviations: SDRA: Acute Respiratory Distress Syndrome; RT-PCR: Reverse Transcription Polymerase Chain Reaction; IVIG: Intravenous Immunoglobulin; PIM-2: Pediatric Index of Mortality-2; IQR: Interquartile Range; TAC: Computed Tomography; CNAF: High-flow Nasal Cannula; CPAP: Continuous Positive Airway Pressure; BiPAP NIV: Non-Invasive Mechanical Ventilation with Bilevel Support; CI: Confidence Interval; OR: odds ratio; PICU: Pediatric Intensive Care Unit; LOS: Length-of-stay

Table 4. Laboratory tests upon admission of pediatric critical patients with confirmed SARS-CoV-2 admitted to the Pediatric Intensive Care Unit (PICU) according to clinical progression (n=219)[a]

Blood-test	Leve/moderado (n = 161)	Severo (n = 58)	Valor p
Hemoglobin, gr/dl	11 (10-13)	10 (9-11)	0.059
Neutrophil count, /mm^3	10335 (7100-15250)	6650 (4800-9217)	< 0.001*
Lymphocyte count, /mm^3	1342 (684-2940)	865 (561-1252)	0.001*
Platelets, /mm^3	239000 (147000-305500)	122000 (78750-203750)	< 0.001*
Creatinine, mg/dl	0.47 (0.31-0.66)	0.56 (0.36-0.85)	0.012*
AST, U/l	38.5 (26-60)	76 (50-119)	< 0.001*
ALT, U/l	30 (17-60)	51 (31-106)	0.001*
LDH, U/l	303 (229-463)	420 (288-654)	0.001*
CRP, mg/dl	10.9 (1.9-25.5)	31 (11.5-111)	< 0.001*
Ferritin, ng/ml	304 (165-610)	534 (286-830)	0.006*
Procalcitonin, ng/ml	0.68 (0.14-2.7)	2.3 (0.48-17.5)	0.005*
INR	1.14 (1.02-1.3)	1.28 (1.1-1.4)	0.002*
D-Dimer, ng/ml	1023 (419-2984)	2610 (620-4000)	0.013*
Troponin, pg/ml	10 (0.1-10.3)	12 (0.3-62)	0.014*
Pro-BNP, pg/ml	415 (96.8-1089.6)	3501 (376-10000)	0.022*

[a]Values reported as median (IQR).*Significant.Abbreviations: AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; PCR: C-Reactive Protein; INR: International Normalized Ratio; Pro-BNP: Pro-B-type Natriuretic Peptide l; IQR: Interquartile range

Table 5. Clinical complications observed in pediatric critical patients with confirmed SARS-CoV-2 admitted to the Pediatric Intensive Care Unit (PICU) according to the type of progression (n = 219)

Clinical Complication	Mild/moderate (n = 161)	Severe (n = 58)	OR (CI 95%)	p Value
Catastrophic pulmonary failure	0 (0)	14 (24.6)		
Hemophagocytic Syndrome	0 (0)	1 (1.8)		
Severe Encephalopathy	0 (0)	3 (5.6)		
Myocarditis	8 (6.3)	10 (18.9)	3.5 (1.3-9.4)	0.014*
DIC	1 (0.8)	1 (1.9)	2.3 (0.15-39)	0.5
Acute Liver Failure	1 (0.8)	4 (7.3)	9.9 (1.1-91.3)	0.029*
Acute Kidney Failure	4 (3.1)	9 (16.7)	6.2 (1.82-21.13)	0.003*
Hyperinflammation	22 (17.2)	26 (46.4)	4.2 (2.1-8.4)	< 0.001*

*Significant. Abbreviations: DIC: Disseminated Intravascular coagulation; IQR: interquartile range; CI: Confidence Interval.

quent, while ARDS was the most frequent in patients admitted due to pneumonia. It is noteworthy that both patients with Kawasaki disease and MIS-C had a similar evolution profile, so it is likely that more than one of the patients initially diagnosed with Kawasaki disease on admission corresponded to MIS-C, a pediatric entity described later in the pandemic, which may be the reason this disease was underestimated in the initial period of the records of this study. Of this cohort, 80% had a chest X-ray and 20% had a pulmonary CT. Chest radiography was normal in 30%, in 38% only an interstitial pattern was observed, and in 18.7% multiple condensations. In patients in whom pulmonary CT was performed, the ground-glass pattern plus condensation was the most frequent, similar to what has been previously described[29]. The overall mortality observed in this series was 3.6%, a lower figure than that reported in a cohort of pediatric critically ill patients hospitalized in different PICUs in our region[16,20,21].

When comparing patients according to the type of

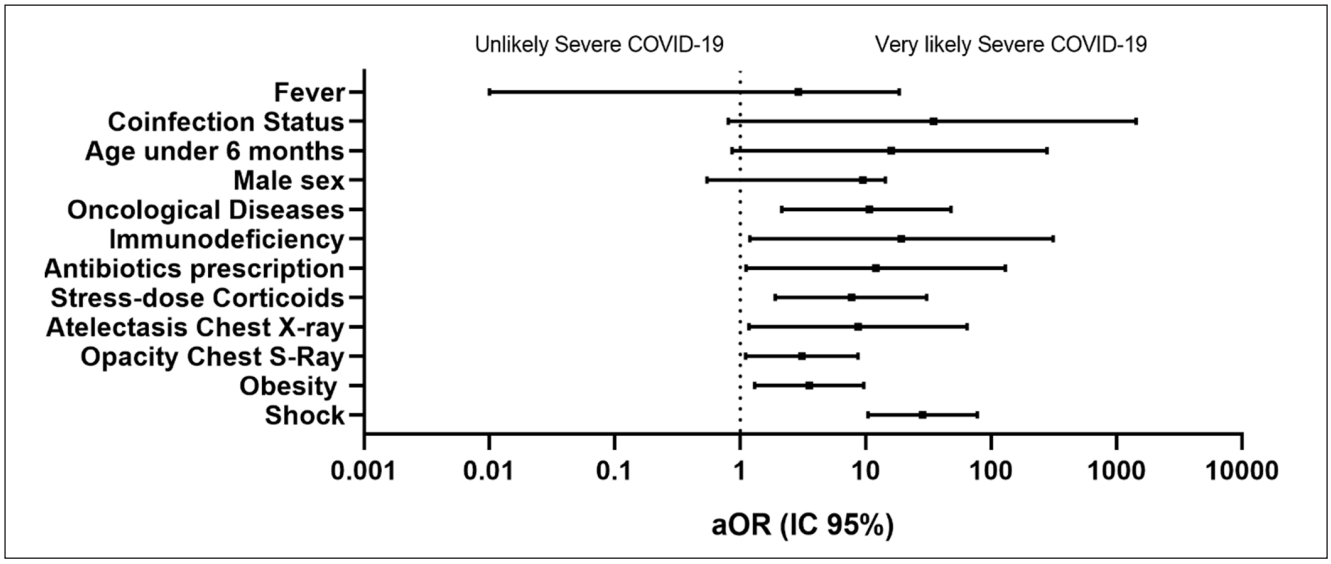

Figure 2. Adjusted Odds Ratios for the outcome of severe COVID-19 in pediatric patients admitted to the Pediatric Intensive Care Unit (PICU). Odds ratios are graphed with a 95% confidence interval and adjusted for sex, younger than 6 months, comorbidities, oncological pathology, obesity, immunodeficiency, chronic lung disease, physical examination retractions, dyspnea, pneumonia or atelectasis on chest X-ray or CT scan, use of antibiotics, stress-dose steroids, co-infection, and shock at the time of admission.

evolution, we found that 26.5% of them were classified as "severe COVID-19", a lower figure than that reported in a Latin American cohort of critically ill patients, which may be because our definition of severity for COVID-19 was stricter than that used in that series[20]. As expected, patients in this group had higher severity scores on admission, developed more shock, ARDS, and organ dysfunction, and required more hemodynamic support therapies and anti-inflammation, anticoagulation, and antibiotic therapy. Similar to what has been described in different reports, patients with "severe COVID-19" had a higher frequency of radiological alterations (pneumonia, atelectasis, and ground glass in the images), laboratory alterations defined by leukopenia, lymphopenia, and increased inflammation markers (CRP, PCT, ferritin, D-dimer), in addition to alterations in liver, renal, and coagulation function tests, with a higher associated mortality[21,25,25,30,31]. Patients with "severe COVID-19" who evolved with severe respiratory failure and who received rescue therapies corresponded mostly (~80%) to those whose admission diagnosis to PICU was pneumonia[30]. Finally, in our cohort, we found that the predictors of developing severe COVID-19 were the presence of shock on admission, radiological condensations, use of corticosteroids in stress doses and antibiotics, acquired/congenital immunodeficiency, oncologic pathology, and obesity, all risk factors mentioned in previous publications[13-15,21,32].

Limitations of this study include the inclusion of patients with confirmed SARS-CoV-2 who were admitted to PICU for monitoring and patients admitted for another pathology in whom SARS-CoV-2 was a screening finding. This could have had an impact on the lower number of patients with severe COVID-19 and the lower morbidity and mortality observed in this study compared with other studies[14,15. 14,15]. Likewise, the non-inclusion of all the PICUs in Chile, because many of the pediatric units in our country were converted for the care of critically ill adults and the non-participation of others, could have led to an underestimation of severe COVID-19 by not considering all the pediatric patients with confirmed SARS-CoV-2 admitted to all the PICU. Also, we did not perform a comparison according to associated SARS-CoV-2 variants during the recruitment period coinciding with the circulation of α (Lineage B.1.1.7), β (Lineage B.1.351), γ (Lineage B.1.1.248 or P1), λ (Lineage C.37), and δ (Lineage B.1.617.1) variants. Despite the above, the strength of this work lies in the active collaboration of the participating centers to describe the clinical profile of an initially unknown virus in the pediatric critical population, making this the first major casuistry study performed in Chile that characterizes pediatric cases hospitalized in PICU due to SARS-CoV-2.

In conclusion, since the beginning of the pandemic, there has been an increase in the literature on SARS-CoV-2 in children. This has allowed us to gain a better understanding of the COVID-19 behavior in this special population. This is the first Chilean characterization of COVID-19 in a cohort of pediatric critically ill patients, whose outcomes were similar

to those described to date in the literature, finding as risk factors for developing severe COVID-19 the presence of comorbidities such as acquired/congenital immunodeficiency, oncologic pathology, and obesity, in addition to presenting shock on admission and opacity in radiological images. It will be important to evaluate in the future how the SARS-CoV-2 vaccine in the national vaccine schedule will impact future results.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: This study was approved by the respective Research Ethics Committee. The authors state that the information has been obtained anonymously from previous data.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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