

Coinfections and comorbidities observed in COVID-19 during the influenza season in the pediatric patient

Coinfecciones y comorbilidad observadas en la COVID-19 durante la temporada de influenza en el paciente pediátrico

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Abstract

Objective: To evaluate if the comorbidity and coinfections presented by SARS-CoV-2 infection vs. COVID-19 impact our Mexican children. **Method:** Prospective and observational study that included the 2020-2021 peak influenza season. All patients with a diagnosis of infection by SARS-CoV-2 vs. COVID-19 who were admitted to the Hospital Infantil de México were analyzed. Real-time RT-PCR for SARS-CoV-2 was performed in all patients, determining E, RdRp and RP genes and protein N, as well as RT-PCR for detection of respiratory viruses. **Results:** The inclusion criteria were met by 163 patients. The group with the highest risk of becoming ill was adolescents (40.4%), followed by schoolchildren and preschoolers (21.4% and 19.6% of the cases, respectively). There were three cases with viral coinfection: two (1.2%) with parvovirus B-19 and one (0.6%) with herpes type I; another two (1.2%) showed bacterial coinfection. The main comorbidity were obesity, acute lymphoblastic leukemia and arterial hypertension. Regarding mortality, we only had four cases (2.4%). **Conclusions:** Obesity, cancer, hypertension, heart disease and diabetes are comorbidity present in our patients, as referred to in literature, but not coinfections. In our study, we did not have any associated mortality related to comorbidity.

Keywords: SARS-CoV-2. COVID-19. Coinfections. Comorbidity. Morbidity. Mortality.

Resumen

Objetivo: Evaluar el impacto de la comorbilidad y de las coinfecciones presentadas por la infección por SARS-CoV-2 vs. COVID-19 en niños mexicanos. **Método:** Estudio prospectivo y observacional que comprendió la temporada alta de influenza 2020-2021, analizando todos los pacientes con diagnóstico de infección vs. enfermedad por SARS-CoV-2 vs. COVID-19 que ingresaron al Hospital Infantil de México. Se realizó en todos RT-PCR en tiempo real para SARS-CoV-2, determinando gen E, gen RdRp, gen RP y proteína N, y RT-PCR multiplex para detección de virus respiratorios. **Resultados:** Los criterios de inclusión los cumplieron 163 pacientes. El grupo con mayor riesgo de enfermar fueron los adolescentes (40.4%), seguidos de los escolares y preescolares (21.4% y 19.6% de los casos, respectivamente). Hubo tres casos con coinfección viral: dos (1.2%) con parvovirus B-19 y uno (0.6%) con herpes tipo I; hubo otros dos (1.2%) con coinfección bacteriana. La principal comorbilidad correspondió a obesidad, leucemia linfoblástica aguda e hipertensión arterial. En cuanto a mortalidad, solo hubo cuatro casos (2.4%). **Conclusiones:** Obesidad, cáncer, hipertensión, cardiopatías y diabetes constituyen la comorbilidad en nuestros

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pacientes, como se refiere en la literatura, no así las coinfecciones. En nuestro estudio no hubo casos de mortalidad relacionada con la comorbilidad.

Palabras clave: SARS-CoV-2. COVID-19. Coinfecciones. Comorbilidad. Morbimortalidad.

Introduction

The first reports of COVID-19 in pediatrics came from Wuhan, China. The initial reports considered that the clinical presentation and the disease *per se*, both in newborns and children younger than 14 years, rarely resulted in severe illness vs adults and young adolescents. The first report from the Chinese Center for Disease Control reported that only 1.3% of 72,314 patients diagnosed with COVID-19 were younger than 20 years¹. The second, a later report of 171 children younger than 16 years hospitalized in Wuhan province, highlighted that only 3 were admitted to the intensive care unit, and only 1 of them died from the disease².

Subsequently, the Morbidity and Mortality Weekly Report by the Centers for Disease Control and Prevention (CDC) of the United States, published on April 6, 2020, stated that 1.7% of nearly 150,000 known cases of COVID-19 in that country were children. There were only 2572 pediatric cases, 15 of which (0.5%) were admitted to an intensive care unit, and similar to the Wuhan report, only 3 (20%) died³.

Since the onset of the coronavirus outbreak in winter 2019 in Wuhan, China we have learned a little more about the epidemiology of COVID-19 in children, but there is still much we do not know about the disease process and, especially, what modifies it⁴. Consequently, various reports have appeared in the literature about the disease in children, associated with co-infection with other respiratory pathogens, meaning pediatric patients infected with SARS-CoV-2 plus 1 or more other respiratory viruses at the same time. In a study of 72 pediatric cases infected, seemingly from domestic contacts, 34 were evaluated for co-infections, and 19 had other viral pathogens besides SARS-CoV-2. Although it is a small study, the high prevalence of co-infections increases the possibility that children share more than one viral infection at the same time⁵.

On the other hand, like adults, children have comorbidities that can increase the risk of severity and even death. In this regard, in a compilation of data on Mexican children diagnosed with COVID-19, the highest prevalence was found in females, with 6983 cases, predominating in both sexes in the 15-19 year-old group, and in younger children, in the 0-4 year-old

group for boys and the 5-9 year group for girls. In Mexico, as of September 30th, 2020, 9.1% (2584/28,388) of pediatric patients with COVID-19 had comorbidity, 19.1% (540/2827) of those hospitalized with COVID-19 had comorbidities, while 26% (83/310) of those who died with COVID-19 had comorbidities⁶.

At the start of this study, we found no national reports on viral co-infections associated with SARS-CoV-2 in Mexican children, so the objective of our study was to observe the presence of viral and bacterial co-infections, the comorbidity presented, and their impact on the progression of the disease in children with COVID-19 admitted to a tertiary pediatric hospital (*Hospital Infantil de México Federico Gómez*).

Method

Study design

This is a prospective and observational study conducted during the influenza season 2020-2021 (weeks 40 to 20), from September 27th, 2020 through May 21st, 2021. We chose this period assuming it is the season for the circulation of influenza and other winter viruses. Patients diagnosed with SARS-CoV-2 infection or COVID-19 disease of both sexes, regardless of age, admitted to *Hospital Infantil de México* were included.

Ethical considerations and inclusion criteria

This study complied with the clinical practice guidelines established by the Declaration of Helsinki on research and ethics. We included in this study all patients who met the criteria for SARS-CoV-2 infection or COVID-19 disease, according to the operational definition of 1 suspected case of viral respiratory disease issued on September 24th, 2020, which states: "Person of any age who in the last 10 days has presented, at least, 1 of the following major signs and symptoms: cough, fever, dyspnea (a sign of severity), or headache along with, at least, 1 of the following minor signs or symptoms: myalgias, arthralgias, sore throat, chills, chest pain, runny nose, anosmia, dysgeusia, and/

or conjunctivitis. In children younger than 5 years-old, irritability may substitute for headache⁷.

Since a diagnostic test is required for all admitted patients, it was not deemed necessary for patients to have an informed consent form or authorization from a parent or guardian at any given time. Similarly, as the study was conducted in a teaching and research hospital, authorization from the ethics committee is not required for observational studies.

Material and methodology

The procedure for taking, processing, identifying, and preserving nasal and nasopharyngeal swab samples was conducted as described below. A viral transport medium (BD Universal Viral Transport), dacron or rayon swabs with plastic shafts (pharyngeal swab), and dacron or rayon swabs with flexible shafts (nasopharyngeal swab) were used for each patient. Nasal and nasopharyngeal swabs were performed on each patient admitted to the COVID-19 area. Both the pharyngeal and nasopharyngeal swabs were placed in the same tube to increase the viral load, ensuring they were transported at a temperature of 2-8°C for processing. Each sample was labeled with the patient's name and surname and was accompanied by the epidemiological study of a suspected COVID-19 case, as indicated by the manual for epidemiological and laboratory surveillance of the Ministry of Health⁸.

Samples were obtained by hospital personnel, both medical and laboratory staff related to the COVID-19 patient care area. Samples were processed to perform the real-time polymerase chain reaction (RT-PCR) test for SARS-CoV-2 using the QuantStudio 5 machine to determine the E gene, RdRp gene, RP gene, and N protein. Additionally, multiplex RT-PCR was performed for the detection of other respiratory viruses, such as influenza A, influenza A (H1N1 pdm09), influenza A (H3N2), influenza B, adenovirus, bocavirus, endemic coronaviruses (OC43, NL63, 229E, and HKU1), metapneumovirus, enterovirus/rhinovirus, and respiratory syncytial virus (RSV).

Results

At the end of the study, we found a total of 173 patients admitted with a diagnosis of SARS-CoV-2 infection or associated disease (COVID-19), 7 of whom were excluded as 3 were adults; in another 6 the diagnosis was not confirmed by laboratory, and in 1 no record was found. Overall, there were 163 patients, showing a

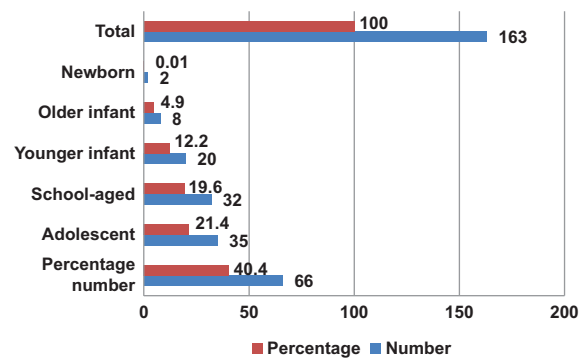


Figure 1. Distribution of cases by age group.

prevalence according to the analyzed period of 4.5%, corresponding to the number of patients seen in the hospital (3591 patients seen from September 2020 through May 2021), and an incidence rate related to the number of patients seen in that same period of 18.1 cases per month and 16.3 per 1000 patients.

Of these 163 patients analyzed, 83 (50.9%) were men, and 80 (49.1%) were women, with the age group at highest risk of illness being adolescents, with 66 cases (40.4%), followed by the group of schoolchildren and preschoolers with 35 (21.4%) and 32 (19.6%) cases, respectively (Fig. 1).

The admitted patients came from different parts of the Republic; however, most came from 2 different states: the State of Mexico and Mexico City, with 81 (49.6%) and 59 (36.1%) cases, respectively. There were other 7 states with a much smaller number of admissions to this hospital (5 [3%], 4 [2.4%], and 1 [0.6%] cases). In only 4 (2.4%) cases was their place of origin unknown (Fig. 2). Considering that we are a hospital located in Mexico City, we saw that most cases came from the Iztapalapa delegation. Notably, the second-largest group was not well determined, as their admission form only listed Mexico City, accounting for 11.8% (7 cases). Two delegations, Venustiano Carranza and Cuauhtémoc, each had 5 cases (8.4%); 3 others had 4 cases (6.7%); 4 had 3 cases (5%); and 1 had only 1 case (1.6%) (Fig. 3).

Regarding observed morbidity and mortality, overall, only 4 (2.4%) cases were recorded, 3/80 (3.8%) women (1.8% of the total) and 1/83 (1.2%) men (0.6% of the total). These data are shown in table 1 and Fig. 4.

Regarding the objectives of this study, co-infections observed in these 163 analyzed patients, we found that only 3 cases (1.8%) with viral co-infection were reported: 2 (1.2%) with parvovirus B-19 and 1 (0.6%)

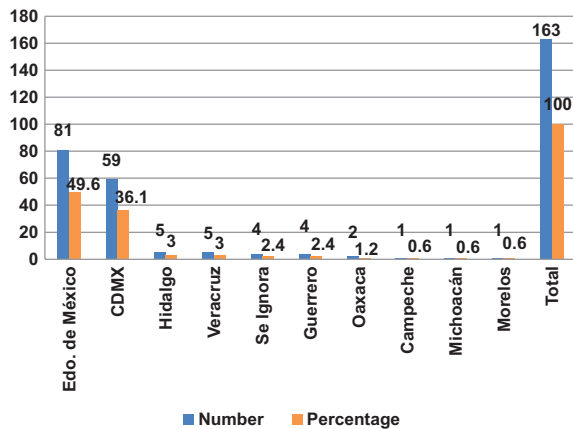


Figure 2. Number and percentage of patients by place of origin.

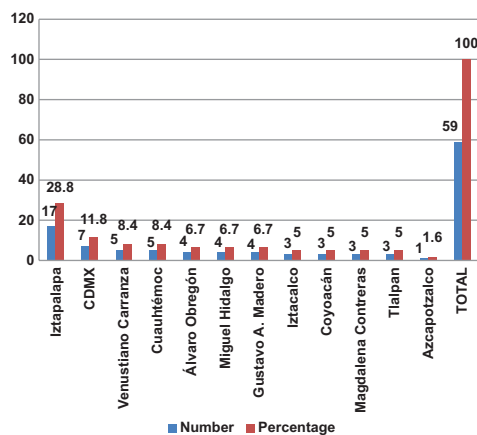


Figure 3. Relationship of cases admitted and percentage by delegation of Mexico City.

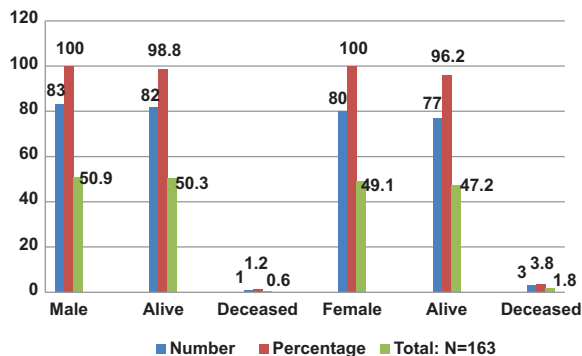


Figure 4. Morbidity and mortality by sex.

with herpes type I. There were other 2 cases (1.2%) with bacterial co-infection, while the rest (96.9%) showed no co-infection (Table 2).

Of note that in the patient with co-infection by herpes type I virus, the diagnosis was only of SARS-CoV-2 infection, with positive nasal and nasopharyngeal swabs for the virus, with RT-PCR results of E gene 20.23, RdRp gene 21.230, and N protein 21.96. Similarly, IgG results were > 1.10 (considered positive). This patient presented with a rash, chest pain, and sore throat. The baseline diagnosis was high-risk acute lymphoblastic leukemia (ALL), and he was admitted for mucositis, infiltrative syndrome, and mucocutaneous lesions confirmed to be caused by herpes type I virus.

The parvovirus B-19 results corresponded to the same patient who had 2 events: the first in September, considered an asymptomatic carrier as the only symptoms were fever, chills, and nasal congestion, with positive nasal and nasopharyngeal swabs, but without a quantitative report from the QuantStudio 5 test; and the second event occurred in October and was considered as SARS-CoV-2 infection associated with reactivation of parvovirus B-19, with positive nasal and nasopharyngeal swabs again, and quantitative report from the QuantStudio 5 test (real-time PCR) of E gene 32.47, RdRp gene 35.400, and N protein 33.93. This patient had hereditary hemolytic anemia as the baseline diagnosis and showed only irritability as a symptom in this second episode. There were no cases of co-infection with any influenza virus.

Regarding comorbidity, we found 8 significant conditions, with obesity being the most prevalent with 24 cases (14.7%); followed by ALL with 18 cases (11.04%), with 8 being high-risk and 7 usual risk; hypertension with 12 cases (7.3%); other malignant tumors and heart disease with 8 cases each (4.9%); and finally, diabetes, Down syndrome, and chronic kidney disease with 7 (5.2%), 6 (3.6%), and 5 (3.06%) cases, respectively. There were 15 other comorbidities with a smaller number of cases (Table 3), as well as 11 cases (6.7%) with other undefined comorbidities and a considerable number of patients without any comorbidity (25.7%; 42/163) (Fig. 5).

Regarding observed mortality related to comorbidity in these patients, we noted that among the 8 main conditions mentioned, no deaths were ever reported (Table 4 and Fig. 6). Although there were 4/163 recorded deaths, these occurred in patients with other types of comorbidities: 1 case with infantile cerebral palsy, 1 with chronic malnutrition, another with chronic malnutrition plus global developmental delay, and 1 with tumor lysis syndrome, along with infiltrative syndrome (considered probable ALL).

Table 1. Morbidity and mortality in cases diagnosed with SARS-CoV-2 infection vs COVID-19 disease

Sex	n	%	Total (n = 163)
Male	83	100	50.9
Alive	82	98.8	50.3
Deceased	1	1.2	0.6
Female	80	100	49.1
Alive	77	96.2	47.2
Deceased	3	3.8	1.8

Table 2. Coinfections observed in patients with SARS-CoV-2 infection vs COVID-19 disease

Co-infections	n	%
Viruses		
None	158	96.9
Herpes type I	1	0.6
Parvovirus B-19	2	1.2
Bacteria		
S. epidermidis	1	0.6
C. difficile	1	0.6
Total	163	100

Discussion

We conducted an observational study, like many reports currently in the literature that describe some events associated with this new COVID-19 infection-disease. In the period mentioned, during which we included the months of high influenza contagion, we found a total of 173 patients, 163 of whom met the analysis criteria. Of these, most were men (83; 50.9%) and the rest were women (80; 49.1%). Regarding age, adolescents ranked 1 in medical assistance (40.4%), followed by schoolchildren and preschoolers, as well as infants (younger [12.2%] and older [4.9%]), and lastly, the group of newborns with only 2 cases being reported (0.01%) (Fig. 1). The origin of the patients was from 10 states of our republic, but in 4 cases (2.4%) their origin was unknown, and from the remaining 9, the State of Mexico and Mexico City were the main places of origin, with 81 (49.6%) and 59 (36.1%) cases, respectively (Fig. 2). Considering that we are a tertiary referral center in Mexico City, we saw that most cases treated were from the Iztapalapa, Venustiano Carranza, and Cuauhtémoc delegations with 17 (28.8%), 5 and 5 (8.4%) cases,

Table 3. Cases with comorbidities associated with SARS-CoV-2 infection vs COVID-19 Disease

Comorbidity	n	%
Obesity	23	14.1
ALL	18	11.04
Hypertension	12	7.3
Other malignant tumors	8	4.9
Heart disease	8	4.9
Diabetes	7	5.2
Down syndrome	6	3.6
Chronic kidney disease	5	3.06
Epilepsy	3	1.8
Malnutrition	2	1.2
Liver diseases	2	1.2
Infantile cerebral palsy	2	1.2
Asthma	2	1.2
Prematurity	2	1.2
Seizures	2	1.2
Juvenile dermatomyositis	1	0.6
Acetyl-CoA deficiency	1	0.6
BPD	1	0.6
Systemic lupus erythematosus	1	0.6
Hemolytic anemia	1	0.6
Esophageal atresia with fistula	1	0.6
HIV	1	0.6
Hemophilia type A	1	0.6
None	42	25.7
Not well defined	11	6.7
Total	163	100

BPD, bronchopulmonary dysplasia. ALL, acute lymphoblastic leukemia. HIV, human immunodeficiency virus

respectively. Similarly, there were 7 cases (11.8%) where the delegation was not specified, and they were simply recorded as coming from Mexico City (Fig. 3).

Mortality was very low, only 2.4% (4/163), corresponding to 3 girls and 1 boy (Table 1 and Fig. 4).

Considering the objectives of this study regarding co-infections in these 163 patients, it is striking that only 5 cases (3.06%) were presented: 3 with viruses (2 parvovirus B-19 and 1 herpes type I virus) and 2

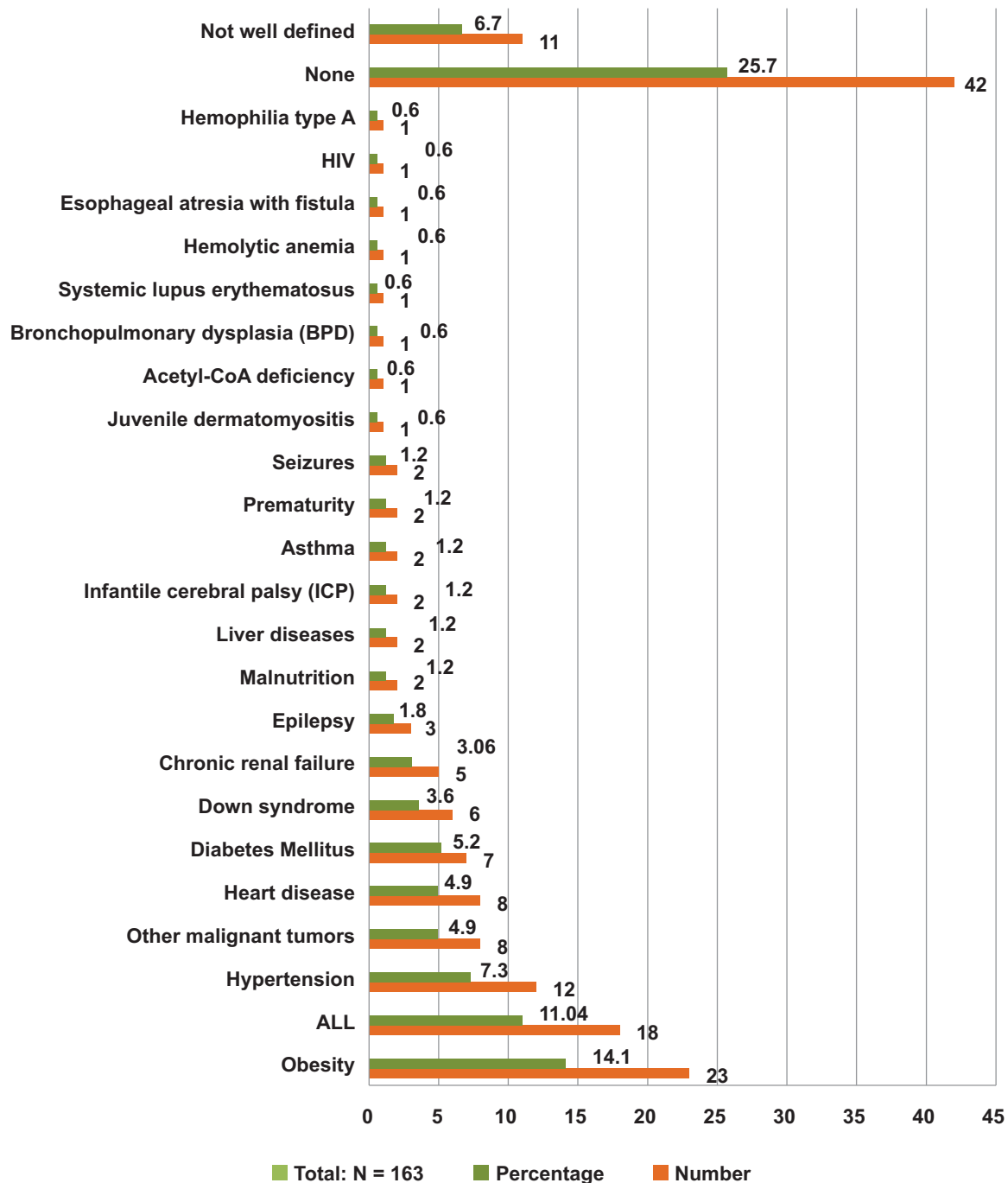


Figure 5. Number and percentage of comorbidities in patients admitted for SARS-CoV-2 infection vs. COVID-19 disease.

bacterial (1 with *Staphylococcus epidermidis* and another with *Clostridioides difficile*) (Table 2 and Fig. 5).

Regarding comorbidity, we found a considerable number of associations in patients infected with SARS-CoV-2 and those who developed COVID-19 disease. The main conditions found as comorbidities were 8: obesity, ALL, systemic arterial hypertension, other

malignant tumors, some type of heart disease, diabetes, Down syndrome, and chronic renal failure; together, they accounted for 51.04% of the total recorded comorbidity. Notably, 25.7% of cases (42) had no associated comorbidities, while in another 11 cases, comorbidities were not defined (6.7%). The remaining ones (16.56%) were cases with diverse

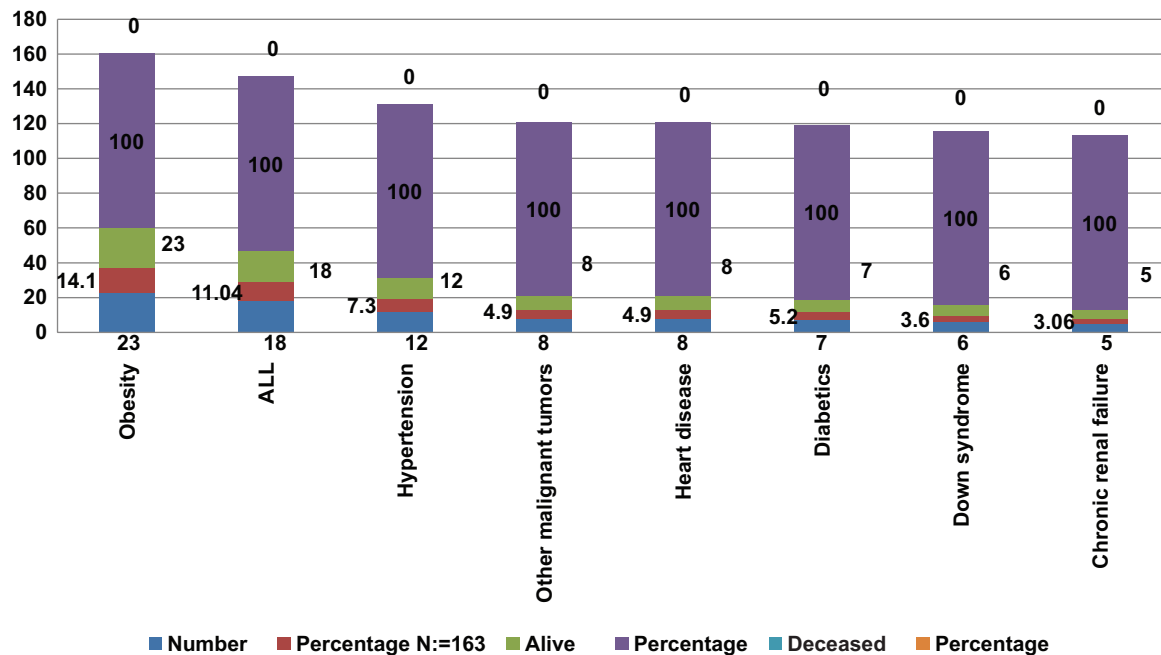


Figure 6. Mortality associated with the main comorbidities in patients admitted to the COVID-19 area.

Table 4. Number and percentage of survivors and deceased with associated comorbidities

Comorbidity	n	% (n = 163)	Survivors	%	Deceased	%
Obesity	23	14.1	23	100	0	0
ALL	18	11.04	18	100	0	0
Hypertension	12	7.3	12	100	0	0
Other malignant tumors	8	4.9	8	100	0	0
Heart disease	8	4.9	8	100	0	0
Diabetes	7	5.2	7	100	0	0
Down syndrome	6	3.6	6	100	0	0
Chronic renal failure	5	3.06	5	100	0	0

ALL: Acute lymphoblastic leukemia

comorbidities in smaller numbers and percentages (Table 3 and Fig. 6).

Although COVID-19 behaves severely or aggressively in patients with comorbidities (especially in young adults and even more so in the elderly)⁹, analyzing the observed mortality relationship with some type of comorbidity, we did not see that relationship in the 8 that stood out as the main ones in our cases (Table 4 and Fig. 6).

Regarding the endpoint of identifying co-infections, as mentioned, there were only five cases, but in one of them, the same co-infection was identified on two occasions, both times presenting with a condition associated with SARS-CoV-2 infection vs. COVID-19 disease, as discussed in the results section. Concerning viral co-infections, it is important to note that there were practically no cases associated with any type of influenza virus, despite having taken the high influenza season 2020-2021 as a study parameter, unlike other studies in the literature mentioning the identification of co-infection cases with RSV, human metapneumovirus, rhinovirus, or parainfluenza virus, among others¹⁰. A study by Wu et al.¹¹ found that in 34/74 children sampled for respiratory pathogens, only 19 (51.4%) had co-infection with *Mycoplasma pneumoniae* (16; 84.2%), RSV (3; 15.8%), Epstein-Barr virus (3; 15.8%), cytomegalovirus (3; 15.8%) or influenza A and B (1; 5.3%). In another report by Kumar et al.¹², 30 analyzed cases of viral and bacterial co-infection were referred, highlighting 12 with *Salmonella typhi*, six with meningitis by *Streptococcus pneumoniae*, three with urinary tract infection by *Escherichia coli*, two with *Salmonella paratyphi* A, two with typhoid fever associated with *Typhus/Rickettsia*, two positive for hepatitis A virus, and one positive for hepatitis E virus, one event of septic arthritis

by *Staphylococcus aureus*, and pneumonia by *S. pneumoniae*⁹⁻¹². The most frequent or common co-infections reported in the literature correspond to bacterial processes, highlighted in 17 studies as more frequent *Mycoplasma pneumoniae* (42%), followed by *Pseudomonas aeruginosa* (12%), *Haemophilus influenzae*, and *Klebsiella pneumoniae* each with 12%¹³. In our study, we only found 2 associated events: 1 with *S. epidermidis* (central venous catheter-associated infection) and 1 with *C. difficile* (chronic diarrhea).

Regarding comorbidities, there may be more studies and with a larger number of cases analyzed. Notably, the difference from the initial reports, one of which¹⁴ only mentioned five cases of children aged 0-16 years admitted to King's College Hospital, in London, United Kingdom, from February 25 through April 28, 2020, indicating that the pre-existing comorbidity included cerebral palsy, prematurity (two cases), Wilson's disease, and dilated cardiomyopathy. However, more recently, a retrospective report¹⁵ with 12,306 children analyzed describes that the main comorbidity consisted of respiratory problems, without specifying which, but were detected in 2310 cases (19.9%), followed by GI events (334; 2.9%), neurological and neuromuscular (252; 2.2%), renal and urological (175; 1.5%), congenital or genetic defects (127; 1.1%), cardiovascular problems (94; 0.8%), metabolic (79; 0.8%), hematological or immunological (57; 0.5%), and malignancies (51; 0.4%). Similarly, a 2021 meta-analysis¹⁶ mentions that the main comorbidities observed in children were obesity, chronic respiratory disease, cardiovascular disease, neurological disorders, immune disorders, metabolic diseases, hematological disorders, cancer, renal failure, and GI conditions. Additionally, as risk factors for severe signs of SARS-CoV-2 disease and risk of death from COVID-19, diabetes, hypertension, and obesity were found, similar to adults, highlighting that obesity was an important factor for developing severe manifestations of SARS-CoV-2 infection and even dying from COVID-19.

Conclusions

To date, there are few reports in the literature on pediatric patients with associated co-infections, but not with present comorbidity, so we consider it important to conduct close monitoring and even a multicenter study of co-infections presented in pediatric patients with SARS-CoV-2 infection vs COVID-19

disease, which would give us an epidemiological and geographical overview of the situation occurring in our Mexican children and we could compare it with what has been reported in the international literature. From the results obtained in our study, we can conclude that co-infections, both viral and bacterial, are uncommon in our hospital. Regarding comorbidities, in line with the main studies that report a large number of analyzed cases, we can say that both obesity and cancer (patients with ALL and various malignant tumors), as well as hypertension, heart diseases, and diabetes, are important conditions presented by our studied patients. However, from what is described in the report by Tsankov et al.¹⁶, in our studied children, no comorbidities represented a risk for death.

Likewise, we consider that based on this study, it might be useful to conduct or evaluate whether at any time of the year a co-infection test should be performed along with a test to detect SARS-CoV-2 infection in all pediatric patients admitted with an acute respiratory condition, or if it should only be done in severely ill patients requiring hospitalization or intubation. Also, if it is suspected or confirmed that a child has RSV or influenza according to the clinical-epidemiological history of contact and initial tests, whether the SARS-CoV-2 test should be performed. These questions might be resolved if a multicenter follow-up study is conducted.

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Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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