

Characterization of pediatric patients with severe community-acquired acute respiratory infections requiring invasive mechanical ventilation

Caracterización de pacientes pediátricos con infecciones respiratorias agudas graves adquiridas en la comunidad que requieren ventilación mecánica invasiva

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

SARIs are one of the main causes of hospitalization in pediatrics and cause significant morbidity and mortality, mainly affecting young infants.

What does this study contribute to what is already known?

In this article, we identify the clinical characteristics of pediatric patients with SARI who require mechanical ventilation, which may help to generate specific interventions for their clinical management, including knowledge of the predominant microbiology and potentially modifiable clinical elements that may improve patient outcomes.

Abstract

Severe acute respiratory infections (SARI) are a leading cause of morbidity and mortality in pediatrics, with high rates of outpatient visits, hospitalizations, and admissions to the Intensive Care Unit (ICU). **Objective:** To describe the clinical and demographic characteristics of pediatric patients with community-acquired acute respiratory infections (CA-ARI) requiring invasive mechanical ventilation (IMV). **Patients and Method:** Retrospective, observational study of patients under 15 years of age admitted to the ICU with a diagnosis of CA-ARI who required IMV between 2019 and 2022 at the *Hospital Dr. Exequiel González Cortés*. **Results:** Overall, 202 patients were analyzed with a median age of 4 months; sex: 63% male. Comorbidity: 47%; median hospital stays: 14 days; ICU stay: 8 days; median MV: 5 days. Identification of virus only (68%), virus and bacteria (18%), bacteria only (3%), and no agent identified (11%). Microbiological identification was successful in 89% of cases. The

Keywords:

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most prevalent virus was Respiratory Syncytial Virus (RSV) (67%), and *Moraxella catarrhalis* was the most common bacterium (29%). RSV was associated with longer IMV time. Healthcare-associated infections: 10%; complications: 40%. Indexed mortality was 1.07. **Conclusions:** Most cases of ARI requiring IMV occurred in infants under 6 months of age and were associated with longer hospital stays and higher complication rates. RSV was the main etiological agent, and there were low bacterial detection rates. It is important to develop strategies to optimize the clinical management of these patients.

Introduction

Severe acute respiratory infections (SARIs) are one of the leading causes of morbidity and mortality in children under 5 years of age, representing a significant public health problem worldwide^{1,2}. They account for approximately 50% of emergency visits and are the leading cause of hospitalization in children under 2 years of age³⁻⁵. It is estimated that 10-22% may require admission to the intensive care unit (ICU), of which up to 25% may require invasive mechanical ventilation (MV)^{6,7}. For these reasons, SARIs continue to be one of the leading causes of mortality in infants and preschoolers⁸, accounting for approximately 13% of deaths in this age group^{5,9}. Although the mortality rate in children under 5 has decreased significantly globally, from 78 to 37 deaths per 1,000 live births between 2000 and 2022^{10,11}, it still exceeds the targets set by the World Health Organization (WHO) and UNICEF to reduce it to less than 20 per 1,000 live births¹². In our country, the decline in respiratory mortality could be associated with multiple public health measures implemented, such as nutrition and immunization programs, clinical protocols for the management of acute respiratory infections in primary care, and advances in pediatric ICUs, all of which have contributed to improving patient survival^{13,14}.

Among the main agents identified in pediatric SARIs, respiratory viruses such as respiratory syncytial virus (RSV), rhinovirus (RV), and metapneumovirus are among the most common^{7,8,15,16}. RSV is responsible for 60-80% of bronchiolitis cases requiring hospitalization, mainly affecting children under 6 months of age, representing 86% of hospitalizations for this cause in this age group^{17,18}. Risk factors associated with SARI caused by RSV include prematurity, chronic lung disease, and/or congenital heart disease, among others^{16,19}. Bacterial etiologies are less prevalent than viral ones, with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes* being the most frequently identified bacteria in all age groups^{9,20,21}.

The requirement for MV for the management of these patients may be associated with potential complications, such as healthcare-associated infections

(HAIs), atelectasis, and extubation failures, among others, which could interfere with the clinical evolution and outcome of patients^{22,23}. For these reasons, identifying the clinical characteristics of pediatric patients with community-acquired SARI on MV is relevant for generating or optimizing specific interventions in the clinical management of this group of patients.

The objective of this study was to analyze the clinical and epidemiological characteristics of pediatric patients with community-acquired SARI who required MV.

Patients and Method

Study design and patients

Retrospective observational study of children under 15 years of age hospitalized due to SARI who received MV support in the ICU of the *Hospital Dr. Exequiel González Cortés* (HEGC) between 2019 and 2022. All pediatric patients with community-acquired SARI admitted to the ICU for MV were included. The following cases were excluded: patients connected to MV due to non-respiratory causes, elective surgery, previous dependence on any ventilatory assistance device (outpatient oxygen therapy, tracheostomized patients and/or those requiring invasive and non-invasive MV), with a history of cystic fibrosis, cancer patients, bone marrow or solid organ transplant recipients, immunosuppressed patients (chronic corticosteroid users, undergoing chemotherapy, HIV patients), as well as those diagnosed with aspiration pneumonia, chemical pneumonia, laryngitis, tracheitis, and/or healthcare-associated pneumonia. Records were obtained by reviewing electronic medical records, creating an anonymized database in Microsoft Excel for the analysis of variables. The following data were collected: sex, age, comorbidities, total days of hospitalization and ICU stay, days on MV, microbiological tests [blood cultures, quantitative tracheal secretion cultures (TSCs), direct immunofluorescence (DIF) of respiratory viruses, and polymerase chain reaction (PCR) for respiratory agents], HAIs, complications (atelectasis, extubation failure, and air leak), pediatric index of mortality

(PIM3), and condition at discharge (alive or deceased). SARIs were classified according to microbiological detection as SARI with viral identification, SARI with bacterial identification, SARI with viral and bacterial identification, and SARI without identified agent. The study was approved by the Ethics Committee of the South Metropolitan Service.

Definitions

SARI: corresponds to an acute respiratory infection with a history of fever or measured fever ≥ 38 °C and cough; with onset within the last 10 days and requiring hospitalization¹. The following ICD-10 diagnoses were considered: J09-J18, J20-22, J40-J47, J60-J98, U07.1, and 7.2.

Microbiology

A search for viral agents was performed using DIF and/or PCR to detect respiratory agents in nasopharyngeal swabs. To identify bacterial agents, the results of blood cultures and quantitative TSCs with a count $> 10^5$ CFU were analyzed. Blood cultures with commensal agents and qualitative TSC were not considered to be of etiological value.

SARI with viral identification: cases in which only viral agents were detected in microbiological studies were included; SARI with bacterial identification: only cases in which bacteria were detected in quantitative TSCs and/or blood cultures were included; SARI with viral and bacterial identification: cases in which the simultaneous presence of viruses and bacteria was confirmed in microbiological studies; SARI without identified agent: patients diagnosed with SARI but in whom the causative agent could not be identified, with negative respiratory panel, TSC, and blood cultures.

MV-free days at 28 days

28 minus days on MV.

ICU-free days at 28 days

28 minus the days of ICU hospitalization.

Indexed mortality

Observed average mortality/expected average mortality.

Extubation failure

Need for reintubation of the patient due to inability to maintain a patent airway and breathe spontaneously within 48 hours after extubation²⁴.

HAIs

Infections are not present or in the incubation at admission, including ventilator-associated pneumonia

(VAP), catheter-related bloodstream infections (CRBSIs), and catheter-associated urinary tract infections (CAUTIs) were recorded.

Statistical analysis

A convenience sample size analysis was performed, including all patients who met the inclusion criteria and excluding those who met the exclusion criteria. A descriptive analysis was performed using medians and interquartile ranges for non-normal continuous variables, and frequencies for categorical variables. Comparisons between groups were performed using the Kruskal-Wallis test and Dunn's post hoc test. Fisher's test was used for categorical variables. Linear and logistic regression models were applied to evaluate adjusted associations, expressing the results as coefficients or odds ratios (OR) with 95% CI. For variables with asymmetric distribution, quantile regression was used. VAP rates were expressed as the number of cases per 1,000 device-days. A p-value < 0.05 was considered significant. The analysis was performed in Stata 14 and IBM SPSS Statistics.

Results

During the study period, there were 814 patients connected to MV in the ICU, of whom 316 were due to respiratory reasons. Of these, 202 (64%) met the inclusion criteria. 63% were male ($n = 128$). The median age was 4 months [interquartile range (IQR) 1-19 months], and 61% ($n = 123$) were infants aged 6 months or younger. 77.8% of patients ≤ 12 months required more than 5 days of MV, compared to 66.9% of those > 12 months, but there was no statistical significance between the two groups ($p = 0.104$). When analyzing age in cases of SARI based on microbiological detection, the medians were 19 months for cases with bacterial identification, 5 months for those with viral and bacterial identification, and 3 months when only viral identification was present. When analyzed according to identified viruses, the median ages were 2 months for RSV, 6 months for metapneumovirus, 9 months for rhinovirus/enterovirus, and 41 months for SARS-CoV-2.

47% of patients had at least one comorbidity ($n = 95$), the most frequent being prematurity (16%, $n = 32$), recurrent wheezing (13%, $n = 27$), and congenital heart disease (6%, $n = 13$). Although the presence of heart disease was associated with a longer median length of hospital stay, no comorbidity was statistically significantly correlated with the length of general hospital stay, ICU stay, or MV. Table 1 summarizes the clinical and demographic characteristics of the patients analyzed, HAIs, and complications, sepa-

rated into the overall population and according to microbiological diagnosis.

The median length of hospital stay was 14 days (IQR = 10-20), 8 days in the ICU (IQR = 5-11), and 5 days on MV (IQR = 3-6) (Figure 1). The days free of MV and ICU at 28 days were 23 days (IQR 22-25) and 20 days (IQR 17-23), respectively. According to the microbiological diagnosis (SARI with viral identification, viral and bacterial, bacterial only, and no identified agent), the median hospital stays were 14, 16, 12, and 10 days; the median ICU stays were 8, 8, 6, and 7 days; and the median MV was 5, 5, 6, and 8 days, respectively. The total days of hospitalization and the identification of the different etiological agents were evaluated, showing statistically significant differences, with longer hospitalization times among patients with SARI with viral and bacterial identification versus those with exclusively viral identification ($p = 0.0125$), as well as among patients with SARI without an identified etiological agent versus those with viral identification and those with bacterial identification ($p = 0.0005$). No significant associations were found between ICU days, age, or other comorbidities with the median number of days on MV.

Microbiological diagnoses were SARI with viral identification (68%), viral and bacterial (18%), bacte-

rial only (3%), and no identified agent (11%). In 89% of cases ($n = 179$), the presence of a virus or bacterium as a possible cause of SARI was demonstrated. At least one virus was detected in 174 patients, the most frequently identified being RSV in 67% of patients ($n = 117$), followed by rhinovirus/enterovirus in 28% ($n = 49$), and metapneumovirus in 15% ($n = 26$) (Figure 2). Viral coinfection was present in 28% ($n = 48$), with the most frequent association being RSV with rhinovirus/enterovirus. The presence of infection by more than one virus was not associated with a significant increase in the number of days of overall hospitalization or ICU stay.

The association between RSV infection and the duration of MV was evaluated using an age-adjusted linear regression model. To reduce confounding biases, the presence of HAIs, comorbidities, and complications was also analyzed, finding an association between RSV infection and a higher number of days on MV (coefficient = 1.70; 95% CI: 0.59 to 2.81; $p = 0.003$).

Of the total number of patients with bacterial identification ($n = 42$), only 7% had positive blood cultures ($n = 3$). The main agents identified in the TSC and/or blood cultures were *M. catarrhalis* (29%, $n = 12$), *H. influenzae* spp (29%, $n = 12$), and *S. pneumoniae* (21%, $n = 9$) (Figure 2).

Table 1. Characterization of patients diagnosed with community-acquired severe acute respiratory infection (SARI) who required mechanical ventilation during the years 2019 to 2022 at HEGC ($n = 202$)

Parameters	Global $n = 202$	Viral $n = 137$	Bacterial- viral $n = 37$	Bacterial $n = 5$
Age in months Median [IQR]	4 [1 – 19]	3 [1-15]	5 [2-12]	19 [2-24]
Age groups n (%)				
< 6 months	115 (57)	88 (64)	20 (54)	2 (40)
6 months to 2 years	46 (23)	25 (18)	11 (30)	1(20)
2 to 5 years	27 (13)	18 (13)	4 (11)	2 (40)
> 5 years	14 (7)	6 (5)	2 (5)	0
Male sex n (%)	128 (63)	86 (63)	25 (68)	2 (40)
Comorbidities n (%)	95 (47)	63 (46)	16 (43)	2 (40)
Nutrition diagnosis n (%)				
Eutrophy	122 (60)	77 (56)	25 (67)	5 (100%)
Undernutrition	52 (26)	42 (31)	7 (19)	0
Overnutrition	28 (14)	18 (13)	5 (14)	0
Global HAIs: n° of events	24	16	5	0
CAUTI (%)	11 (46)	8 (50)	3 (60)	-
CLABSI (%)	7 (29)	4 (25)	1 (20)	-
VAP (%)	6 (25)	4 (25)	1 (20)	-
Complications: n° of events	90	56	20	3
Atelectasis (%)	62 (69)	35 (63)	17 (85)	2 (67)
Extubation failure (%)	16 (18)	13 (23)	2 (10)	0
Air leak(%)	12 (13)	8 (14)	1 (5)	1 (33)
Letality n (%)	3 (1.5)	3 (1.5)	0	0

SARI: Severe acute respiratory infections; MV: mechanical ventilation; HEGC: Hospital Dr. Exequiel González Cortés; IQR: interquartile range; ICU: intensive care unit; HAIs: Healthcare-associated infections; CAUTI: Catheter-associated urinary tract infection; CLABSI: Central line-associated bloodstream infection; VAP: Ventilator-associated pneumonia; N/A: not applicable.

Regarding the presence of the analyzed HAIs, these were reported in 10% ($n = 21$) of patients, with a median hospitalization, ICU stay, and MV duration of 18, 11, and 7 days, respectively (Table 2). A higher risk of developing HAI was observed with increased ICU stay (OR = 1.1; $p < 0.001$; 95% CI: 1.064–1.118) and in patients on MV >5 days (OR = 1.32; $p < 0.001$; 95% CI: 1.159–1.503). The most frequent HAI was CAUTI, with 11 cases (46%); of these, 5 patients were on MV >5 days. There were 6 cases of VAP (25%), 4 of which had MV >5 days. In addition, 7 cases of CRBSI (29%) were identified, with 5 patients on MV for >5 days. The overall rate of VAP was 5.6 per 1,000 days of exposure. When analyzed according to duration of MV, the rate was 6.5/1,000 days in patients with >5 days and 4.3/1,000 days in those with ≤ 5 days of MV, with no statistical difference ($p = 0.63$).

40% of patients ($n = 80$) had at least one complication during their course, with median hospital stays, ICU stays, and MV of 16, 9, and 6 days, respectively

(Table 2). Of these, 53% ($n = 42$) required MV > 5 days. The presence of complications was significantly associated with an increase in the number of days on MV (coefficient = 1.15; 95% CI: 0.21–2.09; $p = 0.016$). The most frequent complication was atelectasis ($n = 62$ patients, 30%).

Regarding the PIM3 score, a median of 1.4 was obtained in the analyzed cohort. During the study period, 3 patients (1.5%) died, with an indexed mortality of 1.07. The median PIM3 among those who died was 3.3. All had viral identification (2 RSV cases); 2 of them were under 6 months of age, with comorbidities, malnutrition, and complications.

During the SARS-CoV-2 pandemic (2020–2021), there was an overall decrease in the number of patients hospitalized due to SARIs (18%, $n = 36$), with no cases of RSV in 2020 (Figure 3), highlighting an increase in the median age (11 months), presence of comorbidity (53%), and increase in HAIs (14%), with no significant differences in hospital stay, ICU stay, or MV.

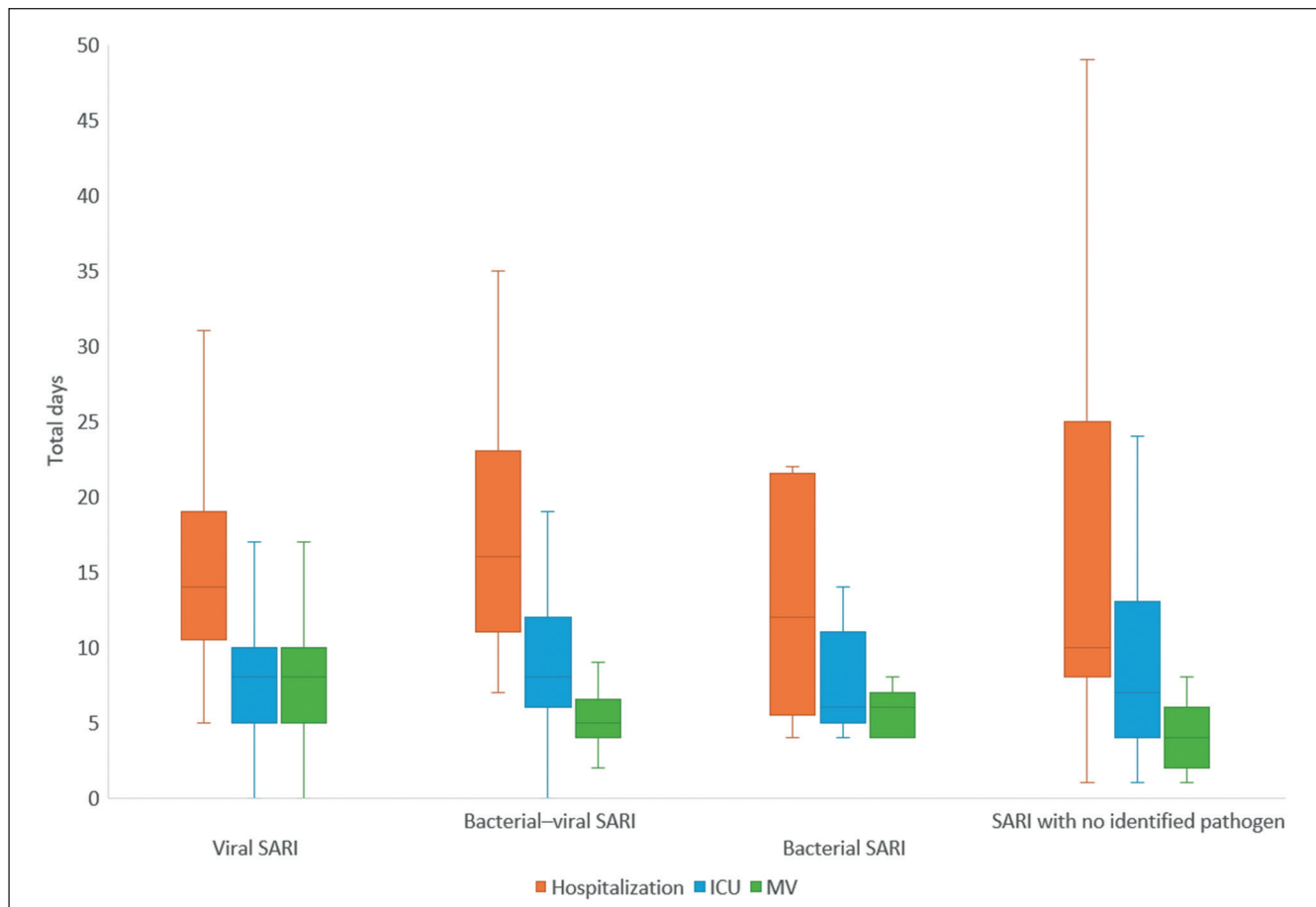


Figure 1. Box-and whisker plot showing the median [IQR] length of hospital stay, ICU stay, and duration of mechanical ventilation according to the diagnosis of viral SARI, bacterial-viral SARI, bacterial SAI, and SARI with no identified pathogen. ICU: intensive care unit; MV: Mechanical ventilation; SARI: severe acute respiratory infection.

Discussion

SARIs remain a major public health problem worldwide, causing significant morbidity and mortality. In our study, the most affected were infants under 6 months of age, similar to what has been described in the literature^{17,26}, with differences in age according to etiology, with medians of 19 months for bacterial agents and 3 months for viral agents, notably 2 months for RSV, 6 for metapneumovirus, and 9 months for rhinovirus, findings that are consistent with other international reports^{6,7,27-30}.

Most patients were previously healthy; however, prematurity, recurrent wheezing, and congenital heart disease were identified as risk factors for worse clinical outcomes, as reported in the literature^{8,19}, without being associated with a significant increase in the length of hospital stay, ICU stay, or MV time.

In our study, the median number of days on MV

was similar to that described in local and international publications, which show stays of 3 to 7 days, with medians close to 5 days in patients with SARI who required MV³¹⁻³⁴. Significant differences in length of hospital stay according to virus and/or bacteria identification could suggest that the etiological origin influences the length of hospital stay, with longer stays in cases of SARI with identified viruses and associated bacteria, compared to those of viral etiology, as reported in other studies³⁵. The days free of ventilation and ICU at 28 days reported by our study (23 and 20 days, respectively) reflect that patients spent most of their hospitalization without requiring invasive MV and with a relatively short ICU stay, which is a novel finding in pediatric reports.

Microbiological identification in SARIs allows therapeutic approaches, such as the use of antibiotics and antivirals, to be guided; however, its determination can be challenging^{36,37}, mainly in bacterial etiologies^{2,5}.

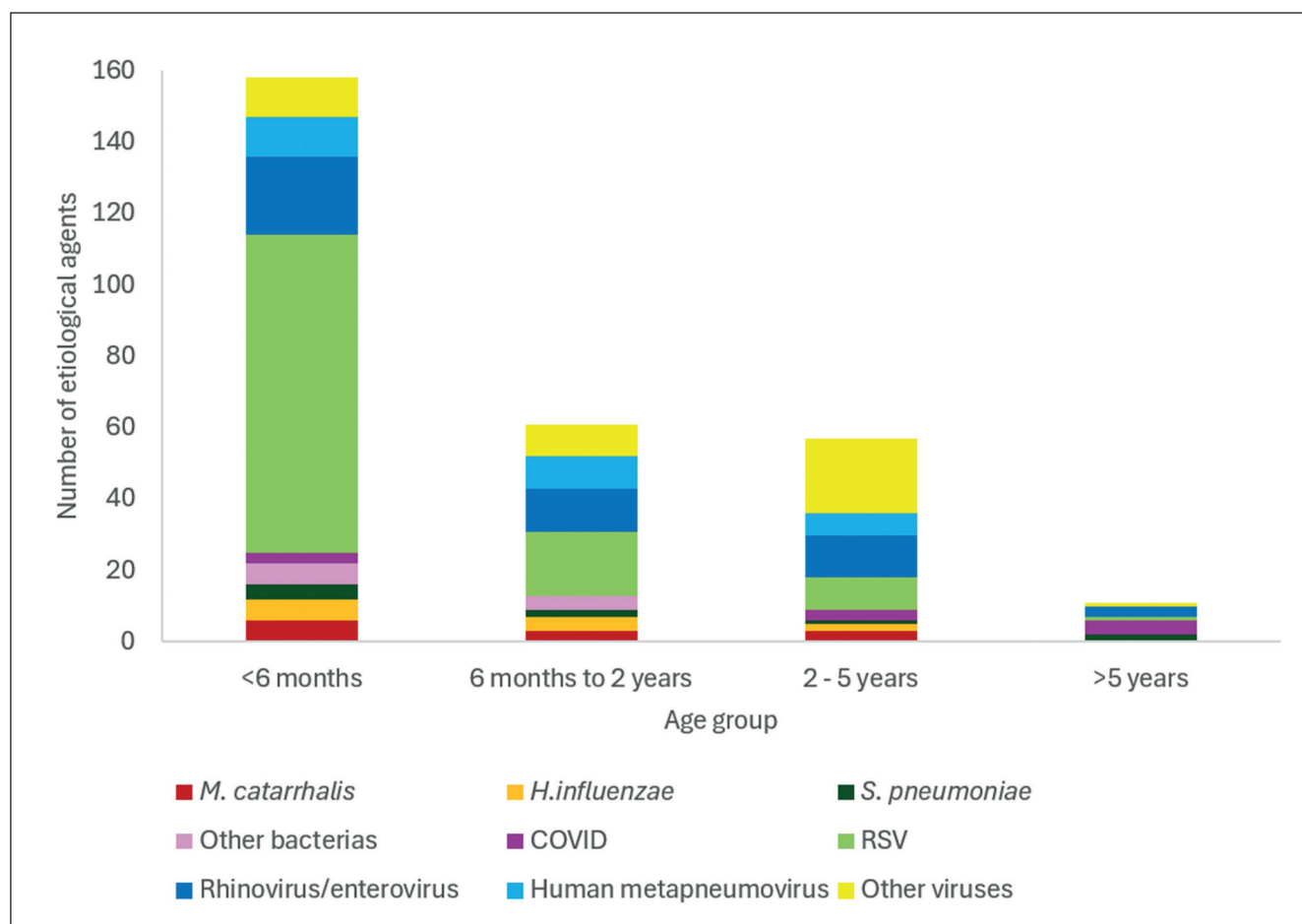


Figure 2. Etiological agents detected according to age group in pediatric patients with SARI requiring mechanical ventilation. MV: Mechanical ventilation; SARI: severe acute respiratory infection; other bacteria: *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Neisseria meningitidis*, *Klebsiella oxytoca*; RSV: respiratory syncytial virus; other viruses: influenza, parainfluenza, adenovirus, bocavirus and non-COVID-19 coronavirus.

Viral coinfection has been described in up to 30% of other studies, similar to what we found (28%), with no differences in prognosis, unlike other studies^{5,16}. Advances in the detection of microorganisms through molecular techniques have made it possible to investigate new agents in patients with SARI, achieving detection in 81-86% of cases^{37,38}. Among these, RSV is the most frequently involved virus in pediatric SARIs^{7,16,28}, being described in up to 46% of patients on MV².

In our study, we found that the presence of RSV infection, whether multiple or isolated, was associated with an increase in days on MV. However, there are multiple factors that could influence this, so further studies are needed to evaluate this association. The fact that no other significant differences in days of MV were found between the different etiologies underscores the importance of identifying potentially modifiable elements that can reduce the duration of MV and allow for earlier weaning, such as serial lung mechanics measuring, avoiding fluid overload,

Tabla 2. Resumen días de hospitalización, días UCI y días de VM en pacientes con IAAS y complicaciones

	Lenght of hospital stay (days)	Lenght of ICU (days)	Lenght of MV (days)
HAI (global)	18	11	7
VAP	19,5	16	9,5
CAUTI	17	10	5
CLABSI	25	13	9
Complications (global)	16	9	6
Atelectasis	16,5	9,5	6
Extubation failure	25	16	8,5
Air leakage	15	9	5

ICU: intensive care unit; MV: Mechanical ventilation HAI: Healthcare-associated infections; CAUTI: Catheter-associated urinary tract infection; CLABSI: Central line-associated bloodstream infections; VAP: Ventilator-associated pneumonia.

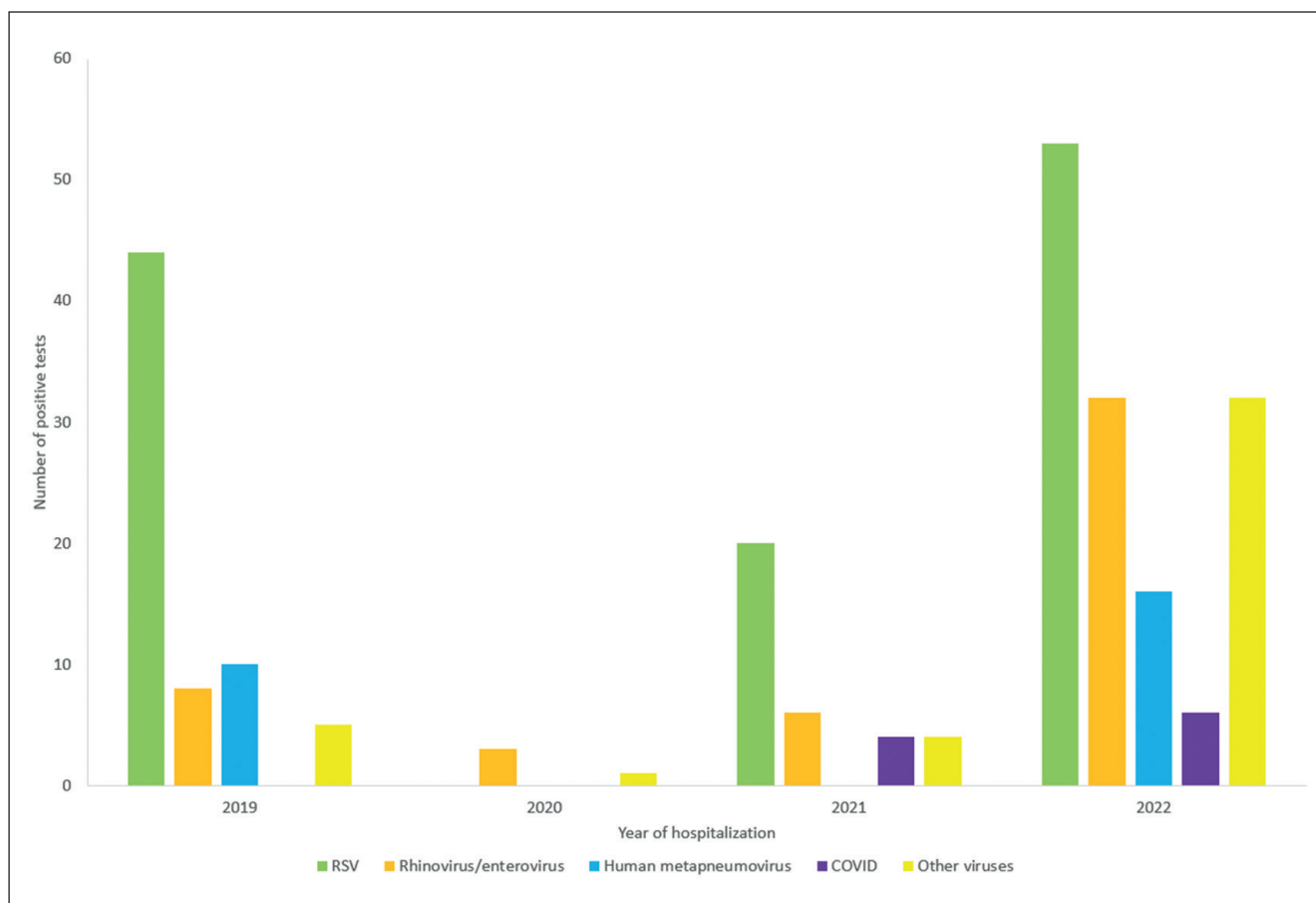


Figure 3. Viral agents detected according to year of hospitalization from 2019 to 2022. RSV: respiratory syncytial virus; other viruses: influenza, parainfluenza, adenovirus, bocavirus and non-COVID-19 coronavirus.

having a sedation-analgesia protocol that can be systematically evaluated using a scale, and reducing risk factors for complications associated with invasive MV³⁹.

Furthermore, the availability of molecular biology has allowed to report rhinovirus as a causative agent of SARI in 21 to 45% of cases⁸, which could be more frequent in countries that have implemented monoclonal antibodies against RSV, such as Chile and Spain, where an effectiveness of 85% and 92%, respectively, was demonstrated for ICU admission^{40,41}, which has had a significant impact on reducing these hospitalizations. However, the morbidity and mortality of patients on MV due to RSV, regardless of their immune status, continue to depend on multiple factors, such as age, comorbidities, duration of MV, and complications, among others.

Bacterial co-infection is common, accounting for 46% to 61% of SARIs^{16,37,42}. However, in our study, we were able to confirm this in only 18% of cases, which may be due to the limited sensitivity of cultures and the low percentage of bacteremia in pneumonia, which has been reported in other studies as less than 5%³⁷. Besides, TSCs should be interpreted with caution, given the commensal and/or colonizing role of bacteria in the respiratory tract^{5,37}. It is important to mention that, despite the low joint detection of viruses and bacteria, 80% of patients were managed by their treating team as mixed infections, with empirical antibiotic regimens, based on a combination of clinical, imaging, and laboratory parameters, which are highly sensitive but nonspecific, making it difficult to analyze them as mixed infections.

Prolonged ICU stay is a known risk factor for the development of HAIs^{22,23,43,44}, similar to what was reported in our study. Additionally, 3% of patients had VAP (rate of 5.8/1,000 device-days), similar to what has been described in other studies. However, there is high variability in these rates, which could reach up to 14/1,000 device-days^{22,43-45}, which could be attributed to several factors, such as the level of surveillance and reporting of HAIs, and sample size, among others. For these reasons, it is essential to establish protocols and strengthen prevention strategies and epidemiological surveillance systems for HAIs, in addition to comprehensive ventilatory management in the ICU to avoid complications in patients on MV. Regarding complications, the most frequent was atelectasis, as in other reports⁴⁶. Extubation failure was associated with an increase in MV time (8.5 days), which is supported in the literature^{24,47}.

Despite their decline in recent years, SARIs remain one of the leading causes of infant mortality^{10,11,48}, which may be due to the implementation of multiple public health measures, such as nutrition

programs, immunization programs, and clinical protocols for the management of acute respiratory infections in primary care, among others^{4,12-14}. Currently, the development of passive immunization strategies against RSV could introduce changes in the future clinical epidemiological profile of patients with SARI on MV. In our study, the case fatality rate was low ($n = 3$, 1.5%), which is consistent with the overall median PIM3 score of 1.4, except in deceased patients, who had a median of 3.3, consistent with their greater severity on admission, such as septic shock, which has been described as an important independent predictor of mortality in patients with severe SARI³⁶ and the presence of comorbidities.

During the SARS-CoV-2 pandemic, a significant decrease in the circulation of other respiratory viruses was observed worldwide due to the multiple epidemiological mitigation strategies implemented⁴⁹, which was reflected in a notable decrease in hospitalizations due to SARI, with a shift to older age and a higher frequency of comorbidities, with no impact on other clinical characteristics such as length of hospitalization, MV, and mortality, suggesting that the impact of SARS-CoV-2 on SARIs was lower in the pediatric population⁴⁹.

Our study has some limitations inherent to its retrospective design, such as registration bias and the lack of comparison with other high-complexity pediatric centers, which do not allow us to assess whether the results obtained could be extrapolated to other ICUs throughout Chile. In addition, due to the lack of a standardized protocol for the diagnosis of mixed SARIs, only cases confirmed by microbiology were considered, so there could be an underdiagnosis of mixed infection due to the low yield of cultures. Despite this, our study has the strengths of having been conducted in a high-complexity pediatric center that serves a large percentage of the country's child population, reports a high number of patients on MV, which could give it representativeness, and is a pioneer in describing the characteristics of patients and etiologies of pediatric SARIs in MV at the national level.

Conclusions

Pediatric SARIs requiring MV are concentrated in infants under 6 months of age, requiring prolonged hospitalizations and presenting high rates of complications. RSV is the main etiological agent, and there is a low yield in the identification of bacterial agents. Given that multiple factors influence the duration of MV, it is key to focus on modifiable factors to reduce hospitalization time.

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: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This docu-

ment is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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