

Age and respiratory syncytial virus etiology in bronchiolitis clinical outcomes



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Background: Respiratory syncytial virus (RSV) is the most frequent cause of bronchiolitis. Precise and updated information about demographic characteristics, clinical manifestations, and risk factors for severe disease are needed for optimal implementation of upcoming new therapeutic and preventive interventions.

Objectives: The main goals of this study were to define the epidemiology of acute bronchiolitis in hospitalized young children during 5 calendar years in Spain; evaluate the differences in clinical manifestations between children hospitalized with RSV infection and those hospitalized with non-RSV infection; and identify demographic characteristics, clinical parameters, and risk factors associated with disease severity.

Methods: We performed a retrospective review of the medical records of children younger than 2 years who were hospitalized with bronchiolitis between January 2015 and December 2019. We constructed multivariable models to identify independent predictors of disease severity defined as length of hospital stay (LOS), pediatric intensive care unit (PICU) admission, and need for a high-flow-nasal canula (HFNC).

Results: From January 2015 to December 2019, 1437 children were hospitalized with bronchiolitis and met the inclusion criteria. The proportion of children hospitalized with bronchiolitis caused by RSV increased significantly during the study period, from 60% to 65% ($P = .03$). The children with RSV bronchiolitis were younger than those with non-RSV bronchiolitis (median age = 3 months [interquartile range = 1.5-6.5 months] vs 4 months [interquartile range = 2-7.5 months], respectively ($P < .01$)). The children younger than 6 months with RSV bronchiolitis had enhanced disease severity compared with those with non-RSV bronchiolitis, as defined by an LOS of more than 4 days, severity scores, need for an HFNC, intravenous fluids, enteral feeding, and PICU admissions ($P < .01$). Age younger than 6 months and RSV-positive etiology were independently associated with greater odds of PICU admission, need for an HFNC, and longer LOS.

Conclusion: This study identified differences in disease severity between young children with RSV bronchiolitis and those with non-RSV bronchiolitis. These differences are particularly significant in children younger than 6 months, who comprise a group of infants with suboptimal innate immunity to RSV and may benefit from new preventive strategies. (*J Allergy Clin Immunol Global* 2022;1:91-8.)

Key words: Bronchiolitis, RSV, epidemiology, age

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Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis; it represents about 60% to 80% of all cases, especially during epidemic peaks. However, several other viruses are associated with bronchiolitis; they include rhinovirus, parainfluenza virus, human metapneumovirus, seasonal coronaviruses, and adenovirus among others.¹⁻³

Previously published studies on the epidemiology and clinical aspects of bronchiolitis in hospitalized patients have reported contradictory results. Different studies conducted in the United States in the 2000s suggested that there was a decrease in the incidence of bronchiolitis hospitalizations.^{4,5} In England, however, the rates of hospitalization for bronchiolitis in infants younger than 1 year increased an average of 1.8% per year between 2004 and 2011, and in children younger than 2 years, higher rates of hospitalization per 1000 children per year were observed between 2001 and 2016.⁶

Despite the burden of bronchiolitis on children's health, specific treatments or vaccines are not yet available. However, it is expected that in the coming years we will have new preventive and therapeutic agents against RSV.^{7,8} Precise and updated information about the demographic characteristics, clinical manifestations,

Abbreviations used

BiPAP: Bilevel positive airway pressure
 CPAP: Continuous positive airway pressure
 HFNC: High-flow-nasal cannula
 IQR: Interquartile range
 LOS: Length of hospital stay
 PICU: Pediatric intensive care unit
 RSV: Respiratory syncytial virus

temporal trends, and risk factors for disease severity in young children of different ages with acute bronchiolitis and with different underlying conditions are relevant for evaluation and clinical implementation of new therapeutic and preventive interventions. This will help define the groups of patients who would benefit the most from these upcoming RSV prevention strategies, such as maternal vaccines and prolonged half-life mAbs.⁹⁻¹⁴

The main goals of this study were to define the epidemiology of acute bronchiolitis in hospitalized young children during 5 calendar years (from January 2015 to December 2019) in Spain, a European country with an excellent and easily accessible public health care system, to evaluate the differences in clinical manifestations between children hospitalized with RSV infection and those hospitalized with non-RSV infection, as well as to identify demographic characteristics, clinical parameters, and risk factors associated with disease severity.

METHODS**Study population**

We conducted a retrospective observational study that included all children younger than 2 years who were hospitalized with a diagnosis of acute bronchiolitis at the Department of Pediatrics of the Hospital Gregorio Marañón over a period of 5 calendar years from January 1, 2015, to December 31, 2019. This pediatric hospital is a university-based tertiary care facility in Madrid, Spain, with more than 1600 children hospitalized in the general pediatric wards every year.

Patients were identified by using the pediatric wards' registry and discharge diagnosis codes. After review of the medical records, only those children with a first episode of bronchiolitis in the first 2 years of life were selected. Patients with incomplete data were excluded.

Data collection

Data were collected from electronic health care records and included epidemiologic, demographic, clinical, and laboratory data, as well as diagnostic test results, disease severity parameters, and interventions during the hospitalization. In addition, we collected data on exposures and the presence of chronic underlying conditions such as the following: prematurity; chronic lung disease; exposure to secondhand smoke; breast-feeding; food allergies; malnutrition; day care attendance; and family history of atopy, asthma, or allergies.

Also, we collected data on the results of laboratory tests (RSV rapid antigen test and Alere BinaxNOW RSV Card [Abbott, Chicago, Ill]); hemoglobin levels; white blood cell counts with differential; C-reactive protein levels; chest radiograph findings; and use of medical interventions such as bronchodilators, systemic steroids, antibiotics, enteral feedings, and intravenous fluids at any time during the hospitalization.

Disease severity was assessed on the basis of a clinical disease severity score (Wood-Downes score modified by Ferré score)¹⁵ and standard parameters of severity, including the following: length of hospital stay (LOS), need for and duration of supplemental O₂ use such as via a nasal cannula or high-flow nasal cannula (HFNC), need for pediatric intensive care unit (PICU)

admission, ventilatory support such as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP), and mechanical ventilation. The disease severity score was assessed at the time of admission. Scoring ranged from 0 (normal) to 14 (most abnormal) and comprised 6 parameters: respiratory rate, heart rate, wheezing, auscultation, cyanosis, and retractions. According to the Wood-Downes score modified by Ferré score, values of 8 or more are considered severe bronchiolitis.¹⁵ Malnutrition was defined as a weight-for-age percentile below the 3rd percentile or *z* score of 2 or lower.¹⁶

Finally, we collected data on pneumonia and atelectasis diagnosed on the basis of radiographic changes as defined by pediatric radiologists. Pneumonia was considered when the radiographic reports included words such as *infiltrate*, *consolidation*, and *pneumonia*. Atelectasis was defined by the presence of volume loss.¹⁷

Statistical analyses

Descriptive analyses were performed by using frequency distributions and rates. Means (\pm SDs) or medians (25th-75th percentiles) were used to summarize patients' demographic and baseline characteristics. The chi-square test for trends was used to determine significant changes in hospitalization rates over time. Comparisons of continuous variables were carried out by using the Student *t* test, Mann-Whitney *U* test, 1-way ANOVA, or Kruskal Wallis test according to data distribution and the number of groups. Comparisons of categorical variables were performed by using the chi-square test or Fisher exact test, as appropriate. The Benjamini-Hochberg test was applied to correct for multiple comparisons when applicable. The relationships between quantitative variables were examined by using the Spearman correlation coefficient. Multivariable models were constructed to identify independent predictors of severity defined as LOS, PICU admission, and need for an HFNC by linear or logistic regression as appropriate. Variables that were significant in univariate analyses ($P < .2$) or were biologically meaningful were introduced in the models. Patients who did not undergo viral testing were excluded from the multivariate models. Associations of risk factors with qualitative variables (HFNC use and PICU admissions) were displayed as odds ratios (ORs) and 95% CIs; for LOS, they were described as risk ratios and 95% CIs, which represent the antilog of the regression parameter estimates and confidence limits. The goodness of fit of the final set of predictors was expressed as the coefficient of determination for multivariate analysis (R^2). We used the Akaike information criterion to compare multivariate models. Assumptions of multicollinearity were evaluated in all models. Statistical analysis was performed by using R statistical software, version 3.5.3.¹⁸ A 2-tailed *P* value less than .05 was considered significant.

Ethical issues

The study was approved by the Hospital Gregorio Marañón institutional review board, with waived informed consent (institutional review board no. CEIC 437/15).

RESULTS**Bronchiolitis admissions and seasonality**

From January 1, 2015, to December 31, 2019, 1437 children were hospitalized for bronchiolitis and met the inclusion criteria. An RSV diagnostic test was performed on 1315 patients (92%), with 838 of them (63.7%) testing positive for RSV. There was a trend toward an increasing proportion of hospitalizations for bronchiolitis in relation to all-cause hospitalizations during the study period, from 16% in 2015 to 19.5% in 2019 ($P = .06$). The proportion of children hospitalized with bronchiolitis caused by RSV increased significantly from 60% to 65% ($P = .03$) (Fig 1, A and B), whereas the percentage of cases of non-RSV bronchiolitis decreased from 38% in 2015 to 34.5% in 2019 ($P = .04$). The highest proportions of hospitalizations occurred in December ($n = 507$ [35.5%]), November (242 [16.8%]), and January (241 [16.7%]). The initial cases of RSV were commonly identified in

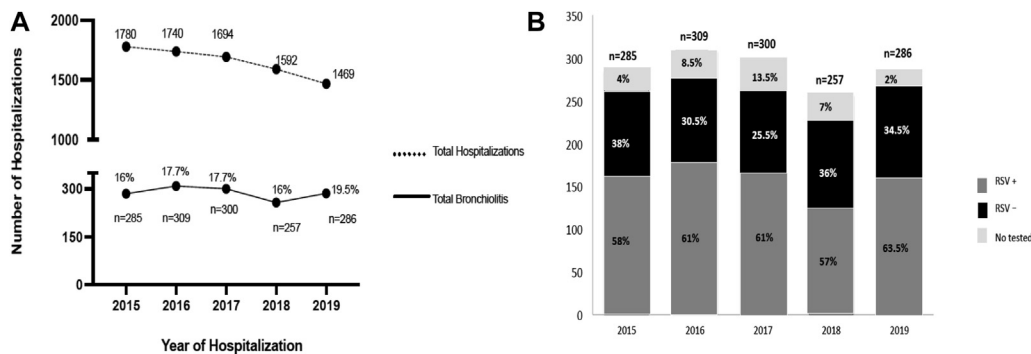


FIG 1. A, Bronchiolitis hospitalizations increased significantly from 2015 to 2019. The x-axis represents each study year. The y-axis reflects the total number of admissions to the infant ward and the total number and percentage of bronchiolitis hospitalizations, which increased from 2015 to 2019 ($P = .06$). **B,** RSV bronchiolitis and non-RSV bronchiolitis hospitalizations in Gregorio Marañón Hospital per year from 2015 to 2019. Hospitalizations attributed to RSV bronchiolitis increased significantly from 2015 to 2019 ($P = .03$).

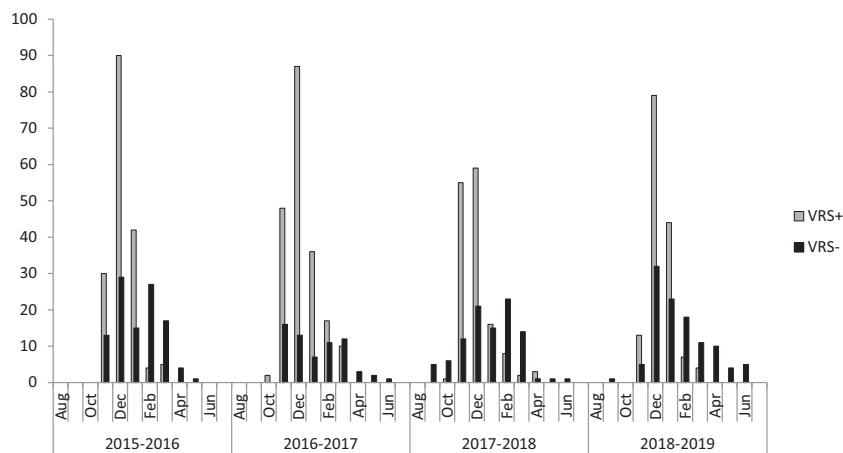


FIG 2. Monthly distribution of hospitalizations for RSV bronchiolitis and non-RSV bronchiolitis. The horizontal axis (x-axis) represents the 4 seasons analyzed and the months of each season; the vertical axis (y-axis) shows the total number of RSV-positive and RSV-negative bronchiolitis cases identified per month during the study period.

the second half of October, and the last cases were identified most commonly in mid-March (Fig 2).

Demographic and clinical characteristics

We included 1437 children younger than 2 years who were hospitalized with bronchiolitis. Overall, the median age of the study patients was 3.0 months (interquartile range [IQR] = 1.5-7 months); 56.6% of the infants were males. The main demographic and clinical characteristics according to their RSV status (RSV-positive vs RSV-negative) are summarized in Table I.

Comparisons between RSV positive and negative children

Among the 1437 children hospitalized with acute bronchiolitis, RSV was detected in 838 (58.3%); the detection rate when we included only those patients on whom a diagnostic test was performed was 63.2% (838 of 1326). Fig 3 shows the main differences between children with RSV bronchiolitis and those with non-RSV bronchiolitis. The children with RSV bronchiolitis were younger than those with non-RSV bronchiolitis (3 months

[IQR = 1.5-6.5] vs 4 months [IQR = 2-7.5] [$P < .01$]). The proportion of children with underlying conditions was significantly lower in the RSV group than in the non-RSV group (22.43% vs 30.39%, respectively [$P < .01$]). No differences were observed in the use of antibiotics between groups; however, among children with documented pneumonia or atelectasis on chest radiograph, the proportion of antibiotic use was lower in children with RSV than in the non-RSV group (77% vs 89% [$P = .03$]). Total white blood cell counts and neutrophil and lymphocyte percentages did not differ significantly between patients with RSV bronchiolitis and patients with non-RSV bronchiolitis (Table I). Disease severity was worse in children hospitalized with RSV bronchiolitis in all parameters evaluated, including the following: longer LOS (5 days [IQR = 3-7 days] vs 4 days [IQR = 2-6 days] [$P < .01$]), higher percentage of children with a Wood-Downes severity score of 8 or higher (36.4% vs 21.3% [$P < .01$]), higher proportion of children requiring an HFNC (37% vs 23.6% [$P < .01$]), need for CPAP/BiPAP (19% vs 8.8% [$P < .01$]), need for mechanical ventilation (2.62% vs 0.8% [$P < .01$]), and higher proportion of PICU admissions (20.7% vs 10.6% [$P < .01$]) (Table I).

TABLE I. Differences between RSV and non-RSV bronchiolitis

Characteristic	Total (n = 1,437)*	RSV (n = 838)	Non-RSV (n = 477)	P value
Demographic characteristics				
Age (mo)	3 (1.5-7)	3 (1.5-6.5)	4 (2-7.5)	<.01
Sex (male)	814 (56.64%)	454 (54.17%)	281 (58.90%)	.82
Malnutrition	295 (20.52%)	153 (18.26%)	114 (23.89%)	.01
Previously healthy	1,059 (73.69%)	650 (77.57%)	332 (69.61%)	.85
Underlying conditions	378 (26.31%)	188 (22.43%)	145 (30.39%)	<.01
Heart disease	33 (2.29%)	16 (1.91%)	14 (2.93%)	
Neurologic disease	22 (1.53%)	10 (1.19%)	11 (2.31%)	
Malformations	17 (1.18%)	8 (0.95%)	6 (1.26%)	
Congenital infections	6 (0.42%)	6 (0.71%)	0 (0%)	
Endocrinologic disease	6 (0.42%)	4 (0.48%)	2 (0.42%)	
Hematologic disease	4 (0.28%)	3 (0.36%)	1 (0.21%)	
Others	10 (0.69%)	6 (0.71%)	3 (0.63%)	
Preterm births	280 (19.48%)	135 (16.11%)	108 (22.64%)	
With other comorbidities	58 (4.10%)	24 (2.86%)	25 (5.24%)	
Without other comorbidities	222 (15.44%)	111 (13.24%)	83 (17.40%)	
Prematurity: gestational age (wk)	280 (19.48%)	135 (16.11%)	108 (22.64%)	<.01
<28	30 (2.10%)	13 (1.55%)	15 (3.14%)	.07
28-31 (+ 6)	41 (2.85%)	11 (1.31%)	21 (4.40%)	<.01
32-36 (+ 6)	209 (14.54%)	111 (13.24%)	72 (15.10%)	.36
Laboratory test results				
Hemoglobin level (g/dL)	11.2 (10.2-12.5)	11.1 (10.2-12.2)	11.2 (10.4-12)	.91
WBC count	11,500 (9,000-14,800)	11,300 (8,750-14,600)	12,200 (9,000-14,550)	.37
Absolute neutrophil count	4,900 (3,200-7,200)	4,800 (3,000-7,000)	5,000 (3,300-7,975)	.41
Absolute lymphocyte count	4,600 (3,400-6,200)	4,650 (3,400-15,300)	4,450 (3,475-6,200)	.84
CRP level (mg/dL)	1.6 (0.5-3.7)	1.65 (0.6-4.15)	1.5 (0.5-3.45)	.42
Radiologic findings				
Radiologic evaluation	579 (40.3%)	359 (42.8%)	183 (38.4%)	.11
No pathologic findings	292 (50.4%)	173 (48.2%)	93 (50.8%)	.58
Atelectasis	46 (7.9%)	37 (10.3%)	8(4.3%)	.02
Focal consolidation	238 (41.1%)	146 (40.6%)	82 (44.8%)	.35
Pneumothorax	3 (0.5%)	3 (0.8%)	0 (0%)	.55
Treatments				
Antibiotics	386 (26.86%)	241 (28.75%)	125 (26.20%)	.33
Bronchodilators	1,113 (77.45%)	617 (73.62%)	392 (82.18%)	<.01
Systemic steroids	131 (9.12%)	59 (7.10%)	60 (12.57%)	<.01
Intravenous fluids	499 (34.72%)	348 (41.52%)	124 (25.99%)	<.01
Enteral feeding	236 (16.42%)	177 (21.12%)	53 (11.11%)	<.01
Parameters of disease severity				
Severity score ≥ 8	433 (30.13%)	305 (36.39%)	102 (21.38%)	<.01
Apnea	173 (12.03%)	108 (12.88%)	60 (12.57%)	.93
LOS (d)	4 (3-5.7)	5 (3-7)	4 (2-6)	<.01
Received O ₂	1,319 (91.78%)	800 (95.46%)	415 (87.01%)	<.01
Duration of O ₂ therapy (d)	3 (2-6)	4 (2-6)	2 (1-5)	<.01
HFNC	448 (31.17%)	310 (36.99%)	113 (23.68%)	<.01
PICU admission	230 (16.01%)	174 (20.76%)	51 (10.69%)	<.01
Time in PICU (d)	4 (2-7)	4 (2-6.5)	3 (2-7)	.09
CPAP/BiPAP	206 (14.33%)	159 (18.97%)	42 (8.81%)	<.01
MV	28 (1.94%)	22 (2.62%)	4 (0.83%)	<.01

This table displays total bronchiolitis cases (ie, RSV bronchiolitis and non-RSV bronchiolitis cases) but patients not tested were excluded. Wood-Downes severity scores higher than 8 are considered severe. The treatment section reflects the need for antibiotics, bronchodilators, steroids, intravenous fluids, or enteral nutrition at any time during admission. In 122 cases, no viral testing was performed. Continuous variables were analyzed by using the Mann-Whitney *U* test, and categorical variables were analyzed by using the Fisher exact or chi-square test. Data are reported as medians and IQRs (25%-75%). Boldface indicates statistical significance.

CRP, C-reactive protein; MV, mechanical ventilation; WBC, white blood cell.

Disease severity in patients with RSV bronchiolitis and non-RSV bronchiolitis according to age

We analyzed whether bronchiolitis severity differed according to age. To this end, we divided the cohort into children younger than 6 months and children older than 6 months. We found that children younger than 6 months with RSV bronchiolitis had enhanced disease severity compared with children with non-RSV

bronchiolitis. Disease severity was defined by an LOS exceeding 4 days, severity scores, need for an HFNC, intravenous fluids, enteral feeding, and PICU admissions ($P < .01$).

Next, we stratified the RSV bronchiolitis and non-RSV cohorts into 4 different age groups: 0 months to younger than 3 months ($n = 577$ [43.9%]), 3 months to younger than 6 months ($n = 317$ [24.1%]), 6 months to 12 months ($n = 282$ [21.4%]), and older

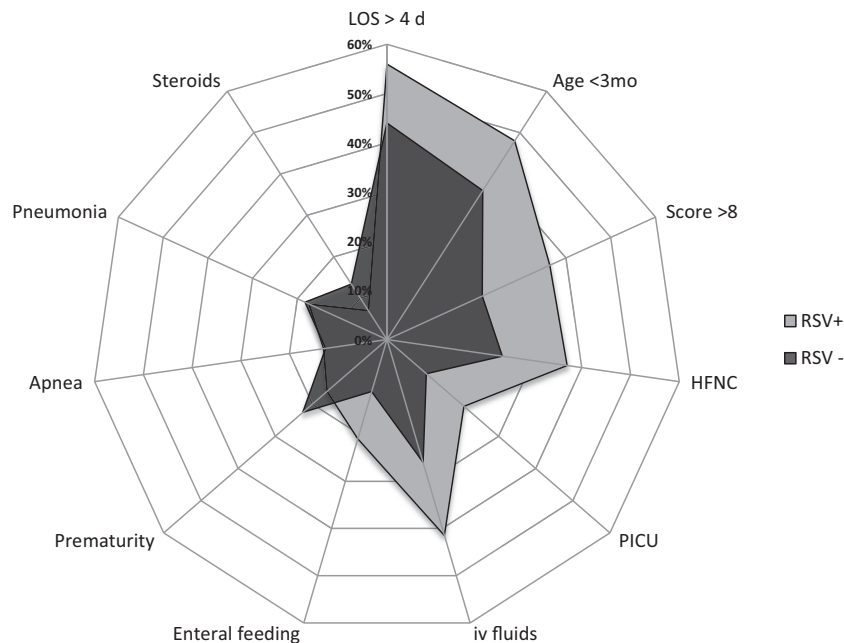


FIG 3. Differences between RSV positivity and RSV negativity. Results were expressed as percentages

than 12 months to 24 months ($n = 139$ [10.6%]) (Table II and Fig 4). Using this approach, we observed that disease severity was greater in infants younger than 3 months of age with RSV bronchiolitis than in those with non-RSV bronchiolitis in terms of LOS (6 days [IQR = 4-9 days] vs 4 days [2-6.2 days] [$P < .01$]), duration of supplemental O_2 use [5 days (IQR = 2-7 days) vs 2 days [IQR = 1-5 days] [$P < .01$]), need for PICU admission (28.6% vs 14.5% [$P < .01$]), need for an HFNC (43.7% vs 26.7% [$P < .01$]), and need for CPAP/BiPAP therapy (26.5% vs 10.5% [$P < .01$]). In addition, the percentage of children with a severity score 8 or higher was greater in the RSV group (43% vs 26% [$P < .01$]) (Table II and Fig 4).

Greater disease severity in children with RSV bronchiolitis was also documented in children between 3 and 6 months of age, who also had a longer duration of supplemental O_2 use (4 days [IQR = 2-6 days] vs 3 days [IQR = 2-5 days], respectively [$P = .04$]) but not in terms of LOS (5 days [IQR = 4-8 days] vs 5 days [4-6 days] [$P = .35$]). The proportion of children requiring an HFNC was higher in the RSV group (38% vs 22% [$P < .01$]) as well as in terms of PICU admissions (18.5% vs 10.5% [$P = .05$]) and the need for CPAP/BiPAP (17.4% vs 9% [$P = .04$]) (Fig 4 and Table II).

When we performed a similar analysis in children between 6 and 12 months of age according RSV status, we did not find significant differences, except for a longer duration of supplemental O_2 use in the RSV group (3 days [IQR = 2-5 days] vs 2 days [IQR = 1-4 days] [$P = .02$]). Differences in disease severity between children with RSV bronchiolitis and those with non-RSV bronchiolitis were no longer identified in children between 12 and 24 months of age. Taken together, these results indicate that bronchiolitis caused by RSV is more severe than that caused by other viruses, especially in infants younger than 6 months.

Independent predictors of disease severity

Lastly, we analyzed which factors were independently associated with disease severity defined by PICU admission, need for an

HFNC, and longer LOS as dependent variables. Age younger than 6 months (OR = 3.03 [95% CI = 1.72-5.26]), RSV positivity (OR = 1.71 [95% CI = 1.01-2.96]), apnea (OR = 3.52 [95% CI = 1.95-6.46]), and lower absolute lymphocyte counts (OR = 1.03 [95% CI = 1.01-1.06]) were independently associated with greater odds of PICU admission (Table III). Likewise, age younger than 6 months (OR = 2.17 [95% CI = 1.58-3.03]), RSV positivity (OR = 1.91 [95% CI = 1.46-2.52]), apnea (OR = 2.25 [95% CI = 1.57-3.24]), malnutrition (OR = 1.71 [95% CI = 1.26-2.32]), and atelectasis (OR = 3.71 [95% CI = 1.59-14.0]) were independently associated with greater odds of HFNC use (Table III). Lastly, we found that age younger than 6 months, malnutrition, apnea, RSV positivity, and documented pneumonia and/or atelectasis were also independent risk factors for longer LOS (Table IV).

DISCUSSION

The present study shows that RSV remains the main etiologic agent of severe bronchiolitis requiring hospitalization during the respiratory season in Spain (November-March) and that the percentage of bronchiolitis caused by RSV increased throughout the study period. We confirmed that RSV bronchiolitis was more severe in terms of LOS, duration of supplemental O_2 use, severity score, PICU admission, and need for an HFNC and ventilatory support, especially in infants younger than 6 months of age. Even in a cohort of hospitalized children only, age had a significant impact in disease severity in children with RSV infection. It is well known that there are currently no effective therapies for the treatment of bronchiolitis, except for the administration of O_2 and respiratory support in the most severe cases (see Table E1 in the Online Repository at www.jaci-global.org).

In agreement with the findings of previous studies, we found that the proportion of hospitalizations for bronchiolitis increased significantly during the study period, from 16% in 2015 to 19.5% in 2019. In addition, the percentage of cases caused by RSV increased from 58% in 2015 to 63.5% in 2019. Other investigators

TABLE II. Differences between RSV and non-RSV bronchiolitis at different ages

Characteristic	< 3 mo			3 to <6 mo			6 to <12 mo			12-24 mo		
	RSV (405)	No RSV (172)	P value	RSV (184)	No RSV (133)	P value	RSV (163)	No RSV (119)	P value	RSV (86)	No RSV (53)	P value
Demographic characteristics												
Sex (male)	48%	38%	.02	46.2%	41.4%	.42	43%	40%	.62	39%	51%	.16
Preterm	12%	17%	.10	20.1%	32.3%	.01	16.6%	25.2%	.09	27.9%	11.3%	.03
Malnutrition	18.6%	24%	.17	15.8%	27.3%	.01	14.7%	23.5%	.06	29%	17.6%	.15
Laboratory test results												
Hemoglobin level	11 (10-12)	11 (10-13)	.44	11 (10-12)	11 (10-11.5)	.10	11 (10-11.5)	11 (10-12)	.56	11(10-12)	12 (11-13)	.68
WBC count (× 10 ³)	10.3 (8-13)	10 (8-13)	.84	12 (9-16)	13 (9-15)	.76	12 (9-15)	13 (10-14)	.52	12 (9-15)	11 (8-16)	.73
Neutrophil count (× 10 ³)	4.1 (2.5-6)	3.7 (2-5)	.74	6 (3-7.6)	5 (4-8.5)	.62	6 (4-8)	6 (4-8.7)	.55	6 (5-9)	6 (4-11)	.91
Lymphocyte count (× 10 ³)	4.7 (3.2-6)	5 (3.5-7)	.33	5 (4-7.1)	4 (3-5.9)	.13	4.6 (3-5)	4.4 (3-6)	.89	4 (3-5)	3 (2 -4)	.60
CRP level	1.5 (0.4-3)	1 (0.2-2)	.52	1.5 (0.6-3)	1 (0.5-2)	.56	2 (0.8-5)	1.9 (0.8-4)	.62	2 (0.7-4)	1.6 (0.7-4)	.73
Radiologic findings												
Radiologic evaluation	150 (37%)	52 (30.2%)	.12	73 (39.7%)	55 (41.4%)	.80	85 (52.1%)	56 (47%)	.46	51 (59.3%)	20 (37.7%)	.01
No findings	89 (59.3%)	29 (55.8%)	.74	24 (32.8%)	29 (52.7%)	.04	43 (50.6%)	30 (53.6%)	.73	17 (33.3%)	5 (25%)	.58
Atelectasis	19 (12.7%)	4 (7.7%)	.45	14 (19.2%)	4 (7.3%)	.07	4 (4.7%)	0 (0%)	.15	0 (0%)	0 (0%)	.99
Focal consolidation	40 (26.7%)	19 (36.5%)	.21	35 (47.9%)	22 (40%)	.47	37 (43.5%)	26 (46.4%)	.86	34 (66.7%)	15 (75%)	.57
Pneumothorax	2 (1.3%)	0 (0%)	.99	0 (0%)	0 (0%)	.99	1 (1.2%)	0 (0%)	.99	0 (0%)	0 (0%)	.99
Treatments												
Antibiotics (%)	20%	19%	.73	25%	26%	.89	39%	32%	.31	53%	34%	.03
Bronchodilators	65%	69%	.47	73%	85%	.01	87%	94%	.02	88%	93%	.72
Systemic steroids	0.5%	2.5%	.06	2.5%	8.5%	.03	11%	21%	.02	37%	39%	.85
Intravenous fluids	43.5%	28.5%	<.01	44.6%	21.8%	<.01	35%	28.6%	.30	38.5%	22.7%	.07
Enteral feeding	28%	12%	<.01	21.2%	13.5%	.10	12.3%	10%	.70	6%	2%	.40
Parameters of disease severity												
Severity score ≥ 8 (%)	43%	26%	<.01	36.4%	22%	.01	32%	22%	.14	24%	15%	.32
Severity score	5 (4-9)	5 (4-8)	<.01	5 (4-8)	5 (4-6)	<.01	5 (4-8)	5 (4-6)	.27	5 (4-7)	5 (4-6)	.84
Apnea	22%	25%	.84	8%	9%	.81	1.5%	3.5%	.24	2.3%	0%	.52
LOS	6 (4-9)	4 (2-6.2)	<.01	5 (3-7)	5 (3-8)	.35	4 (3-7)	4 (2-6)	.08	4 (2-6)	3 (2-5)	.14
Duration of O ₂ (d)	5 (2-7)	2 (1-5)	<.01	4 (2-6)	3 (2-5)	.04	3 (2-5)	2 (1-4)	.02	3 (1-5)	2 (1-3)	.10
HFNC	43.7%	26.7%	<.01	38%	22%	<.01	27%	21%	.26	22.1%	22.6%	.90
PICU admission	28.6%	14.5%	<.01	18.5%	10.5%	.05	9.8%	9.2%	.90	9.3%	1.9%	.15
Time in PICU (d)	4 (2-7)	3 (2-7)	.29	4 (2-5)	3 (2-5)	.44	3 (1-4)	2.5 (2-4)	.76	5 (2-9)	3 (3-3)	.80
CPAPP/BiPAP	26.5%	10.5%	<.01	17.4%	9%	.04	8%	9.25%	.82	8%	1.9%	.15
MV	4.2%	1.7%	.21	2.2%	0%	.14	0%	0.8%	.42	1.2%	0%	.90

This table displays total bronchiolitis cases (ie, RSV bronchiolitis and non-RSV bronchiolitis cases). The treatment section reflects the need for antibiotics, bronchodilators, steroids, intravenous fluids, or enteral nutrition at any time during admission. Continuous variables were analyzed by using the Mann-Whitney *U* test, and categorical variables were analyzed by using the Fisher exact or chi-square test. Data are reported as medians and IQRs (25%-75%). Boldface indicates statistical significance.

CRP, C-reactive protein; MV, mechanical ventilation; WBC, white blood cell.

previously found an increase in rates of hospitalizations for bronchiolitis during the periods 2002-2007 and 2001-2016,^{6,19,20} although yet other authors have reported reductions in hospitalization rates.^{4,5,11}

We found that 73.69% of children hospitalized with bronchiolitis had no underlying medical conditions. In addition, RSV-positive infants had a lower percentage of underlying conditions than did those with non-RSV bronchiolitis (22.4% vs 30.3%). These results are in agreement with those of Garcia et al,¹⁹ who also found a major proportion of underlying conditions in the non-RSV group, which likely reflects the implementation of prophylaxis with anti-RSV mAbs in the high-risk groups. In addition, the detection of RSV as a cause of bronchiolitis was associated with less frequent antibiotic administration. Perhaps, the lack of knowledge of the etiologic agent in cases of respiratory infection led physicians to prescribe antibiotics more frequently in those cases. This observation provides another important argument to encourage viral testing in patients hospitalized for bronchiolitis.

A recent study⁹ reported that age differences had a significant impact on clinical manifestations and severity in children with RSV bronchiolitis. The study highlighted the importance of age stratification to better understanding of this disease and its pathogenesis. In the present study, when we stratified the patient cohorts by age groups and according to RSV status, we found significant differences in most of the parameters of disease severity analyzed (LOS, duration of O₂ therapy, PICU admission, need for an HFNC, and need for mechanical ventilation). Young infants (ie, those younger than 3 months) who were RSV positive had a more severe disease, and the differences in disease severity parameters were documented until 6 months of age. This is consistent with the findings of other studies in which younger infants were at higher risk of need for supplemental O₂ administration and PICU admission.^{11,21-26} These clinical data are correlated quite precisely with improved understanding of the infant's immune system, in which the innate immune response against RSV, especially the interferon response, does not appear to be protective until after 6 months of age.^{27,28}

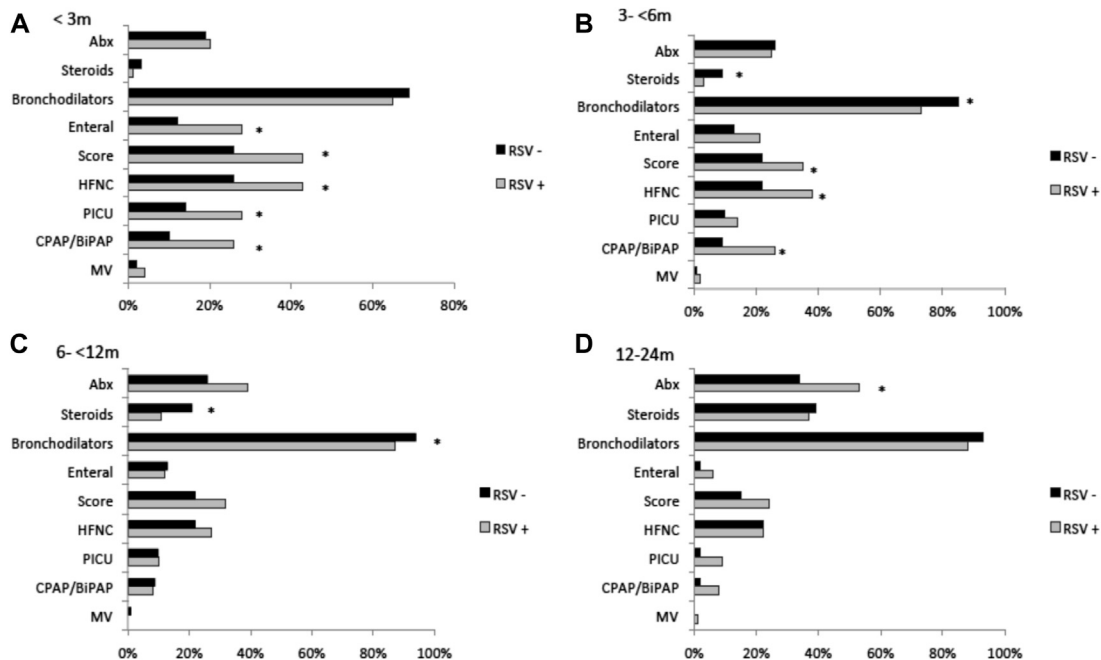


FIG 4. Treatments and parameters of disease severity according RSV status and stratified age. All items were stratified according RSV (blue) versus no RSV (orange) and by age younger than 3 months (A), between 3 and 6 months (B), older than 6 months to 12 months (C), and older than 12 months to 24 months (D). The y-axis represents the treatments and parameters of disease severity in the 2 groups, and the x-axis represents the frequency of each item (%). Comparisons were done by using the Fisher exact test. Asterisk indicates significant 2-sided P values. This figure reflects only the treatments administered during the time of admission. Bronchodilators were always used via inhalation. Abx, Need for antibiotics at any time during admission; MV, mechanical ventilation.

TABLE III. Risk factors for PICU admission and need for HFNC determined by multivariate logistic regression analysis

Characteristic	Need for PICU admission/HFNC		
	PICU admission		
	OR	95% CI	P value
Age < 6 mo	3.03	(1.72-5.26)	<.01
Sex (male)	1.15	(0.73-1.81)	.53
Malnutrition	1.69	(0.98-2.90)	.05
Apnea	3.52	(1.95-6.46)	<.01
RSV	1.71	(1.01-2.96)	.04
Low absolute lymphocyte count	1.03	(1.01-1.06)	<.01
	Need for HFNC		
Age < 6 mo	2.17	(1.58-3.03)	.01
Malnutrition	1.71	(1.26-2.32)	.01
Apnea	2.25	(1.57-3.24)	<.01
RSV	1.91	(1.46-2.52)	<.01
Atelectasis	3.71	(1.59-14.0)	<.01

For the first model (with PICU admission as the dependent variable), $R^2 = 0.30$ and Akaike information criterion = 472.13; for the second model, (with need for HFNC as the dependent variable), $R^2 = 0.40$ and Akaike information criterion = 1228.1. Both models were made by excluding those patients not tested for RSV (122 patients). Boldface indicates statistical significance.

These results demonstrate the importance of thoroughly analyzing the impact of age on this disease, as new preventive interventions such as vaccines and prolonged half-life mAbs are being evaluated in clinical trials.⁹ In this new era, it is essential to define the burden of disease in each subgroup of patients rather than only in those at high-risk, because the new prolonged half-life mAbs and maternal vaccines are directed to all at-term

TABLE IV. Risk factors for LOS determined by multivariate lineal regression analysis

Characteristic	Risk ratio	95% CI	P value
Age < 6 mo	5.26	2.95-9.10	<.01
Malnutrition	3.98	2.84-5.59	<.01
Apnea	6.76	4.44-10.2	<.01
RSV	3.04	2.27-4.05	<.01
Pneumonia/atelectasis	7.46	3.96-10.81	<.01

$R^2 = 0.28$; F statistic (5) = 44.97.

Age, RSV, apnea, malnutrition and pneumonia/atelectasis were analyzed as categorical variables in relation with LOS. Associations of risk factors in lineal regression were displayed as ratios and 95% CIs, which represent the antilog of the regression parameter estimates and confidence limits. Boldface indicates statistical significance.

previously healthy infants, who represent approximately 70% to 80% of hospitalized children, as shown in the present study. Having precise and updated clinical information in terms of disease severity of the different age groups will be important to guide decisions for the implementation of these new prevention strategies.^{7,8,29,30} An additional challenge is to also obtain similar accurate data for outpatients with RSV infection so as to better define the burden of disease in this important subgroup.

Adjusted analyses confirmed that younger age, RSV etiology, apnea, and lymphopenia were independently associated with disease severity. Other authors^{31,32} have reported an association between lower lymphocyte counts and worse disease severity in previously healthy infants younger than 12 months with RSV bronchiolitis. Similarly, lymphopenia has been identified as a risk factor in other viral infections such as COVID-19 or

influenza.^{33,34} Nevertheless, information regarding the role of lymphopenia in bronchiolitis disease severity is still limited. In our data set, lymphopenia was barely significant as an independent risk factor for PICU admission, suggesting that low lymphocyte counts are indeed associated with worse clinical disease severity.

Our study has several limitations. The definition of bronchiolitis is controversial; in this study we have included infants as old as 24 months, even though other definitions suggest including only infants no older than 12 months. Our study's retrospective design may have introduced some bias due to missing data. In addition, no viral diagnostic studies were performed outside the respiratory season, and even during the epidemic period we only performed an RSV-specific test. Thus, the RSV-negative group is not well characterized, and we were unable to analyze the role of viral coinfections. Nevertheless, the number of cases analyzed during the 5-year period allowed us to identify important and clinically relevant differences between children with RSV bronchiolitis and those with non-RSV bronchiolitis.

In conclusion, this study identified differences in disease severity between young children with RSV infections and those with non-RSV infections, and it showed that these differences are especially significant in children younger than 6 months. The majority of children hospitalized with RSV bronchiolitis during the 5 study seasons were previously healthy and without any apparent risk factors. Infants younger than 6 months of age with or without risk factors for severe RSV infection constitute an important group that may benefit from novel preventive strategies.

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