RSV and exposure to cigarette smoking as risk factors for severe bronchiolitis in a tropical country

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Abstract

Objetive: This study aims to identify risk factors associated with severe bronchiolitis in children. In a retrospective cohort study, we included all infants younger than two years of age in tertiary centers in Rionegro, Colombia, hospitalized due to bronchiolitis from January 2019 to December 2019. Severe bronchiolitis was defined as rhinorrhea, cough, tachypnea, wheezing, rales, and increased respiratory effort (e.g., grunting, nasal flaring, and intercostal and/or subcostal retraction), with symptoms of severity (e.g., increased respiratory rate, retractions, and oxygen saturation at 90% or lower). To identify factors independently associated with severe bronchiolitis, we used log-binomial regression and estimate prevalences ratio (PR) and adjust for potential confounding variables

Results: Of a total of 417 included, 300 (72.12%) have severe bronchiolitis. After modeling and controlling for potential confounders in the multivariate analysis: RSV isolation (PR 1.15 95%CI 1.03–1.29) and current exposure to cigarette smoking (PR 1.19 95%CI 1.04–1.35) were independent predictors of severe bronchiolitis. We concluded that RSV and exposure to cigarette smoking are independent predictors of severe bronchiolitis. These potentially modifiable variables associated with severity should guide future interventions to reduce the morbidity and economic burden of bronchiolitis in our population.

Introduction

Bronchiolitis is the most common cause of hospitalization in pediatric patients worldwide (1). Among inpatients with bronchiolitis, approximately a quarter have severe bronchiolitis (2, 3). The high medical cost associates with severe bronchiolitis impose a relevant economic burden, especially in tropical middle-income countries (4, 5). Some models have identified predictors of severe bronchiolitis such as age, underlying conditions (congenital heart disease, chronic lung conditions, and immunocompromised states), low weight, male gender, clinical characteristics at admission, prematurity and RSV isolation (6). A systematic review of the psychometric properties of eleven predictive models or scales to assess the severity of the disease, reveals that current bronchiolitis assessment tools lack established reliability and validity and may not be sensitive to clinically meaningful outcomes for patients (7). In this context, there is a critical need, especially in tropical middle-income countries, for explores risk factors for severe bronchiolitis in each population, which allows determining which clinical, laboratory or imaging characteristics are associated with this condition and thus help decision-making in the emergency setting. This study aims to identify clinical variables associated with severe bronchiolitis in children in tropical middle-income countries.

Methods

We conducted a retrospective cohort study that included all infants with bronchiolitis younger than two years of age in tertiary centers in Rionegro, Colombia, from January 2019 to December 2019. Rionegro is a city in Antioquia, Colombia, located in the subregion of Eastern Antioquia, at an average elevation of 2,125 meters above sea level. The average annual precipitation varies between 1,800 and 2,500

millimeters with an average temperature of 17 °C. The municipality of Rionegro had a total population of 101,046 inhabitants, with two tertiary referral hospitals(8). Inclusion criteria were defined as children younger than two years of age admitted to the pediatric ward diagnosed with bronchiolitis, according to the national clinical guideline of bronchiolitis (first wheezing episode younger than 24 months of age (9). Patients without lower respiratory compromise, with positive bacterial cultures on admission, confirmed whooping cough (culture or PCR) were excluded. The study protocol was reviewed and approved by the Institutional Review Board of the University of Antioquia (No 18/2015).

Procedures : Medical records of all patients admitted to the emergency department were reviewed. We collected the following variables: age, sex, weight, height, signs, and symptoms on admission (including fever, chest indrawing, chest auscultation, %SpO2), vaccination scheduled chart for age, current exposure (maternal o paternal) to cigarette smoking, history of prematurity and bronchopulmonary dysplasia confirmed by a neonatologist at the time of discharge from the NICU, comorbidities (congenital heart disease, neurological disease), diagnostic tools as chest X rays, hemograms, etc. Additionally, we collected variables related to outcomes of care or disease-severity parameters such as length of hospital stay. In our hospitals, bronchodilators and systemic steroids are used at the discretion of attending physicians according to national clinical guidelines of bronchiolitis (9). Also, children are transferred to the PICU if they have worsening hypoxemia or hypercapnia, respiratory distress, inspired fraction of oxygen more than 50%, hemodynamic instability, or apnea. NPA was taken immediately upon admission to the emergency department within 48 hrs of admission using standardize technique. RSV was confirmed using direct immunofluorescence (Light Diagnostics TM Respiratory Panel 1 DFA, Merck-Millipore Laboratory).NPA data for other viruses were no available in our institution consistently

Outcome definition: Severe bronchiolitis was defined as increased respiratory rate, retractions, and oxygen saturation at 90% or lower) (10)

Statistical analysis: Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range [IQR]), whichever appropriate. Categorical variables are shown as numbers (percentage). Differences between continuous variables were analyzed using the unpaired t-test or Wilcoxon's signed-rank test, whichever was appropriate. Associations between categorical variables and the outcome variable were analyzed using the chi-square test or Fisher's exact test, as needed. To identify factors independently associated with severe bronchiolitis, we used log-binomial regression and estimate prevalences ratio (PR) and adjust for potential confounding variables. Log-binomial regressions provide correct estimates PR and are a better alternative for the analysis of cross-sectional studies with binary outcomes than logistic regression; PR is a better measure of the association than odds ratio when the prevalence of event is high (11, 12). We only include initially variables associated with severe bronchiolitis with values of $p < 0.2$ or that changes the effect estimate by more than 10% after their inclusion. The variable selection and modeling processes were made following the recommendations of Greenland(13). The goodness of fit of the model was evaluated using the Hosmer–Lemeshow test. All statistical tests were two-tailed, and the significance level used was $p < 0.05$. The data were analyzed with Statistical Package Stata 15.0 (Stata Corporation, College Station, TX).

Results

Study population: During the study period, 417 cases of bronchiolitis were included. 66% of the patient was less than 6 month, most of them males (60%), with O2 supportive (83%), RSV was isolated in 200 patients (48%). 81 patients had a history of premature birth and 17 of them with BPD. 20 patients had some cardiac o neurological disease and 10 of them with a history of use of palivizumab. 49 patients (12%) referred to current exposure (maternal o paternal) to cigarette smoking. The median of the length of hospital stay was 3.68 days, with a range of 0.74 days to 29 days and an interquartile range of 4.06 days. In Table 1 is presents the clinical characteristics of the population.

Table 1
Demographic features and clinical information of the patients included in the study

Variable. n(%)	n (%)
Age less than 6 month	277(66.43)
Male, n(%)	251(60.34)
Premature birth	81(19.47)
Comorbidities (CHD or neurological)	20(4.81)
BPD	17(4.09)
Atopy	17(4.09)
Previously hospitalization by bronchiolitis	30(7.21)
Exposure to cigarette smoking	49 (11.9)
Complete vaccination for age	415(99.5)
Exclusive maternal breastfeeding for at least six month	102(24.4)
SpO2, median(ds)	89(0.28)
O2 supportive, n(%)	347(83.41)
Clinical & laboratory parameters	
Respiratory rate	41(13.35)
Fever	119(28.61)
Chest indrawing	184(44.23)
Tachypnea	48(13.30)
Rhonchi	137(32.93)
Crepitation	137(32.93)
Abnormal X-ray*	109(26.33)
Leucocytosis (> 15.000/mm3)	51(12.26)
RSV positive	200(48.48)
Increased C-reactive protein (> 4 mg/lit.)	327(78.61)
Outcomes	

*Atelectasis (n = 7), alveolar(n = 16) or interstitial (n = 48) infiltrates, hyperinflation(n = 38)

CHD : Congenital heart disease, BPD: Bronchopulmonary dysplasia, PICU: pediatric intensive care unit admission, RSV: Respiratory syncytial virus

Variable. n(%)	n (%)
Severe hypoxemia	115 (27.58)
Length of hospital stay, median (range)	3.68(0.74-29)
pneumonia	80(19.23)
Sepsis	19(4.57)
Atelectasis	8 (1.92)
Pneumothorax	1(0.24)
PICU	55(13.22)
*Atelectasis (n = 7), alveolar(n = 16) or interstitial (n = 48) infiltrates, hyperinflation(n = 38)	
CHD : Congenital heart disease, BPD: Bronchopulmonary dysplasia, PICU: pediatric intensive care unit admission, RSV: Respiratory syncytial virus	

Multivariate analysis of predictors associated with severe bronchiolitis : Among all 417 patients, 300 (72.12%) have severe bronchiolitis. As mentioned above, to identify factors independently associated with severe bronchiolitis, we used log-binomial regression. The predictive variables included in the complete model were age, sex, premature birth, comorbidities, BPD, atopy, parental smoking, previously hospitalization by bronchiolitis, %SpO2, fever, signs of respiratory distress, RSV, Leucocytosis (> 15.000/mm3) and increased C-reactive protein (> 4 mg/lit.). After modeling and controlling for potential confounders in the multivariate analysis: RSV isolation and parental smoking were independent predictors of severe bronchiolitis (Table 2).

Table 2
Final model of log-binomial regression analysis

	PR	CI 95%	p
RSV isolation	1.15	1.028−1.297	0.015
Exposure to cigarette smoking	1.19	1.045−1.355	0.008

Discussion

The main purpose of this study was clinical variables associated with severe bronchiolitis in children in tropical middle-income countries with bronchiolitis. Our study shows that RSV and parental smoking were independent predictors of severe bronchiolitis. While some predictors of severity, such as age, comorbidities, and maybe initial signs of respiratory distress, cannot be modified, others as RSV isolation and parental smoking are potentially modifiable by interventions such as futures vaccines or palivizumab in high-risk population or smoking cessation interventions in parents. Respect to the association between

RSV and severity, previous studies in other populations had revealed the importance of RSV as a predictor of the severity of the disease. Dumas, et al analyzed data from two prospective, multicenter cohorts of children younger than 2 years hospitalized with bronchiolitis, one in the USA (2007–2010 winter seasons, n = 2207), and one in Finland (2008–2010 winter seasons, n = 408). Using latent class analysis, found that in the profiles with wheezing at ED presentation and profile with the most severely ill group with the longer hospital were associated with a higher probability of RSV infection in USA and Finland. (14). Rodriguez et al, in a retrospective cohort study of 6344 children with acute lower respiratory infection in Colombia, during 2 years (2009–2011), found that mixed RSV-adenovirus was a predictor of severe disease (RR 2.09; CI 95% 1.60–2.73; P < 0.001). DeVicenzo et al, in a sample of 141 infants < 24 months old without previous chronic cardiac or lung disease or prematurity, in Tennessee found that higher nasal RSV load was an independent predictor of longer hospitalization. A 1-log higher RSV load predicted a 0.8-da longer hospitalization, reflects the higher RSV load that occur earlier in the disease (15–17). Mansbasch et al, in a prospective cohort of 2207 infants of 16 US hospital without excluding patients previous chronic cardiac or lung disease or prematurity, also found that patients with RSV have a higher proportion of patient with severity and prolonged LOS (> 3 days) than patients with only HSV infection but less than RSV + HRV infection (48% vs 28% vs 54%, p < 0.001), and in the multivariate model presence of RSV + HRV was an independent predictor of length of stay > 3 days among children with severe bronchiolitis(18). Rodríguez-Martínez in 303 infants with acute bronchiolitis in Bogota, also found that RSV isolation correlated with a hospital stay of 5 or more days (OR 1.92, CI 95% 1.02 to 3.73)(19). The actual evidence supports a strong association between decreased cellular immunity and severe RSV bronchiolitis, suggesting that a maturation-related defect of the cellular immune system facilitates severe RSV. A low level of cellular and humoral immunity would explain that higher viral titers are found in infants with the most severe illness (20).

In our study, exposure to cigarette smoking was an independent risk factor associated with severe bronchiolitis. This result is consistent with those from previous studies that reported children's exposure to maternal cigarette smoking increased the risk of hospitalization in infants and young children with bronchiolitis. Robledo-Aceves et al, in a retrospective study, in Mexico, included 134 children 2 years or younger with severe viral bronchiolitis, and 134 healthy age-matched. Its study report that exposure to cigarette smoking was independently associated with hospitalization for severe bronchiolitis in the multivariate analysis (OR, 3.5; 95% CI, 1.99–6.18; P = .0001). Bradley et al, in a prospective study of 206 hospitalized infants, all under 12 months old with bronchiolitis in Missouri, found that maternal smoking were independent predictors of reduced O2 Saturation (OR, 2.3; 95% CI, -0.05, – 4.66; P = .05)(21). Chatzimichael et at, in 40 consecutive infants with bronchiolitis aged from 6 to 24 months in Greece, found using a multivariate regression analysis that exposure to environmental tobacco smoke (OR = 2.2, 95% CI = 1.1–3.6) showed significant association with severe bronchiolitis and prolonged hospitalization (22). Farzana et al, in Farzana in a case-control study of 128 infants with bronchiolitis (64 cases and 64 controls) found that parental smoking carried 2.8 times the risk of developing severe bronchiolitis (OR 2.8,95% CI 1.36 t-5.72). Cigarette smoke exposure decreased cyclic adenosine monophosphate levels and increased phosphodiesterase-4 enzymatic activity, resulting in increased airway hyperresponsiveness,

which may explain the potential mechanism by which smoke exposure decreases lung function and severe bronchiolitis (23).

Limitations.

Our study has limitations. First, since this study was based on medical records review, we cannot include other variables such as environmental pollution and genetic factors, and residual confounding cannot be excluded. Second, the study was conducted in a tertiary referral hospital, and therefore the patients included represent the high spectrum of severity, limiting the generalization of results to other contexts. However, the similarity of our population in terms of clinical characteristics, risk factors, and seasonality of bronchiolitis in our country with previous reports suggest strength and consistency in our results(5, 19). Third, in our study, we used an immunofluorescence assay for the diagnosis of RSV infections that, despite being widely available, being easy to perform, but we did not determine the RSV genomic load, and also we did not test for viruses. This can generate some differential misclassification bias, which could have overestimated the true association between RSV isolation and the outcome variable, however, the previous evidence in other populations had confirmed this association being plausibility our results.

Abbreviations

CHD : Congenital heart disease, BPD: Bronchopulmonary dysplasia, PICU: pediatric intensive care unit admission, RSV: Respiratory syncytial virus

Declarations

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