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Predictors of prolonged length of hospital stay for infants with bronchiolitis

Carlos E Rodríguez-Martínez^{1,2}, Monica P Sossa-Briceño³, Gustavo Nino⁴

¹Department of Pediatrics, School of Medicine, Universidad Nacional de Colombia, Bogotá, Colombia

²Department of Pediatric Pulmonology and Pediatric Critical Care Medicine, School of Medicine, Universidad El Bosque, Bogotá, Colombia

³Department of Internal Medicine, School of Medicine, Universidad Nacional de Colombia, Bogotá, Colombia

⁴Division of Pediatric Pulmonary, Sleep Medicine and Integrative Systems Biology, Center for Genetic Research, Children's National Medical Center, George Washington University, Washington, District of Columbia, USA

Abstract

Among inpatients suffering from bronchiolitis, approximately a quarter may undergo a prolonged length of stay (LOS) for the treatment of their respiratory condition. However, there have been few research studies that have evaluated variables that may be associated with a prolonged LOS in these patients, especially in low-income and middle-income countries, where the clinical and economic burden of the disease is the greatest. In an analytical single-center cross-sectional study, we included a population of patients with acute bronchiolitis hospitalized between March and June 2016. We collected demographic and clinical information and the LOS of each patient. Prolonged LOS for bronchiolitis was defined as at least one hospital stay of 5 or more days. A total of 303 patients were included, with 176 (58.1%) male and a median (IQR) age of 3.0 (1.0–7.0) months. After controlling for gender, history of bronchopulmonary dysplasia, number of days with respiratory symptoms, the presence of apnea as an initial manifestation of bronchiolitis, and other underlying disease conditions, we found that the independent predictors of prolonged LOS for bronchiolitis in our study population included age (OR 0.92; 95% CI 0.84 to 0.99; $p=0.049$), history of prematurity (OR 6.34; 95% CI 1.10 to 36.46; $p=0.038$), respiratory syncytial virus isolation (OR 1.92; 95% CI 1.02 to 3.73; $p=0.048$), and initial oxygen saturation (OR 0.94; 95% CI 0.88 to 0.98; $p=0.048$). The factors identified should be taken into account when planning policies to reduce the duration of hospital stay in infants with bronchiolitis.

Correspondence to: Dr Carlos E Rodríguez-Martínez, Department of Pediatrics, School of Medicine, Universidad Nacional de Colombia, Bogotá, 11010, Colombia; carerodriguezmar@unal.edu.co.

Contributors CER-M conceptualized and designed the study, carried out the final analyses, drafted the initial manuscript, and approved the final manuscript as submitted. MPS-B and GN designed the data collection instruments, carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Patient consent Not required.

Ethics approval Institutional Review Board.

INTRODUCTION

Acute bronchiolitis is the most important cause of lower respiratory tract infection in children during the first 2 years of life and is the leading cause of hospitalization for infants beyond the neonatal period.¹ Although in general acute bronchiolitis is a self-limited condition that can be managed conservatively at home without significant medical care, a non-negligible proportion of children often require hospitalization for observation and supportive therapy.² Among inpatients suffering from bronchiolitis, approximately a quarter may undergo a prolonged length of stay (LOS) for the treatment of their respiratory condition.^{3,4} Hospitalized bronchiolitis imposes a significant clinical and economic burden,⁵ particularly in low-income and middle-income countries (LMICs),^{6,7} and this burden is even greater when patients require a prolonged LOS.⁸ Hospital LOS is directly associated with bronchiolitis hospitalization costs, and there are reports indicating that these costs are responsible for nearly two-thirds of the total economic impact of the disease.⁹ With the growing emphasis on high-value medical care, as well as efforts to measure and improve the quality of healthcare, LOS is now largely considered to be a measure of the quality of health service and a quality of care/performance indicator.¹⁰ In addition, prolonged LOS has been associated with significant psychologic and emotional impact on the patients, as well as on their families and caregivers, and a greater probability of inpatient complications such as hospital-acquired infections, which in turn can lead to an even greater LOS.¹¹

Despite its undoubted importance, prolonged LOS is an outcome measure that has received little attention in previous analyses of patients suffering from bronchiolitis. Although prior studies have identified factors associated with prolonged LOS among infants admitted with bronchiolitis, which can be grouped as birth-related factors (prematurity),¹² underlying conditions (congenital heart disease,¹³ chronic lung conditions,¹⁴ immunocompromised states¹⁵), adverse clinical events (nosocomial infections,¹⁶ mechanical ventilation,⁹ intensive care unit admission, feeding problems, and duration of supplemental oxygen¹⁷), clinical characteristics at admission (age,⁹ level of respiratory distress,^{18,19} and presence of hypoxia³ or apnea²⁰), and interventions given during the early hospital course (number of times suctioned,⁴ and the use of deep suctioning and the lapses between suctioning events²¹), there have been few research studies that have evaluated variables that may be objectively measured at admission or early in the hospitalization in LMIC, where the clinical and economic burden of the disease is the greatest. Accordingly, the aim of the present single-center study was to determine predictors of prolonged LOS in a hospitalized population of Colombian children suffering from acute bronchiolitis.

MATERIALS AND METHODS

Study site

Bogota, the capital city of Colombia, a tropical LMIC located in South America, has one-fifth of Colombia's population and is located at an elevation of about 2650 m (8660 ft) above sea level. Although respiratory syncytial virus (RSV), the most commonly identified virus in infants with bronchiolitis, is active in the city throughout the year, it peaks during the 3-month period from March to May, the first rainy period of the year in the city.²² The

Fundación Hospital de La Misericordia is a tertiary-care, university-based children's hospital located in the metropolitan area of Bogotá that mainly functions as a referral center, admitting about 12,000 children per year (of which about 2000 are due to bronchiolitis), and it registers more than 60,000 emergency room visits per year (of which about 3000 are due to bronchiolitis). The majority of admissions to the hospital come from the emergency department (ED) and from inpatient transfers from outlying primary and secondary clinics and hospitals. The high rate of hospitalizations for bronchiolitis is mainly due to the regional and national referral nature of the hospital.

Study design and procedures

We conducted an analytical single-center cross-sectional study that included a random sample of patients aged <2 years with a diagnosis of acute bronchiolitis hospitalized in the Fundación Hospital de La Misericordia between March 2015 and April 2016. We chose this time period because it roughly coincides with the main bronchiolitis season in the city.²² Medical records of patients hospitalized for bronchiolitis were reviewed for the following demographic, clinical, and microbiologic information: date of admission, age (months), gender (male, female), birth weight (<2500 g, 2500 g), occurrence of breast feeding for at least 6 months (yes, no), number of days with respiratory symptoms (less than 24 hours, between 24 and 48 hours, between 48 and 72 hours, more than 72 hours), RSV isolation (yes, no), the presence of apnea as an initial manifestation of bronchiolitis (yes, no), initial oxygen saturation (continuous variable), history of prematurity (defined as a birth prior to 37 weeks' gestational age), bronchopulmonary dysplasia (defined as oxygen dependence at 36 weeks of postmenstrual age), and other underlying disease conditions such as previous respiratory disease (recurrent wheezing or pneumonia), congenital heart disease, and underlying neurologic disease (yes, no). In our institution, all children hospitalized for acute lower respiratory infections are routinely tested for RSV using a rapid immunochromatographic test method (RSV Respi-Strip; Coris BioConcept, Gembloux, Belgium).

Outcome definition

Prolonged LOS for bronchiolitis was considered to be the main measure of the outcome. Prolonged LOS for bronchiolitis was defined as at least one hospital stay of 5 or more days in a general ward and/or in a pediatric intensive care unit for acute bronchiolitis (International Classification of Diseases (ICD)-10 codes J21, J21.0, J21.1, J21.8, and J21.9). Although there is no validated definition of what constitutes a 'prolonged' LOS for bronchiolitis, we consider that a hospital stay of 5 or more days is a reasonable cut-off for considering a hospital stay for bronchiolitis in infants as prolonged, because this value is above the 75th percentile of LOS reported in the literature⁴¹⁷¹⁹²³ and is comparable with the 75th percentile of LOS of patients hospitalized in the Fundacio Hospital de La Misericordia with a diagnosis of acute bronchiolitis.²⁴

Statistical analysis

Continuous variables are presented as mean±SD or median IQR, whichever is appropriate. Categorical variables are presented as numbers (percentage). Differences between continuous variables were analyzed using the unpaired t-test or the Mann-Whitney U test,

whichever was appropriate. Associations between categorical variables were analyzed using the χ^2 test or Fisher's exact test, whichever was appropriate. To identify factors independently associated with prolonged LOS for bronchiolitis, we adjusted logistic regression models. Variables that were considered to be able to influence the duration of LOS for bronchiolitis, such as age, gender, birth weight, occurrence of breast feeding for at least 6 months, number of days with respiratory symptoms, RSV isolation, the presence of apnea as an initial manifestation of bronchiolitis, initial oxygen saturation, and the presence of underlying disease condition, were selected a priori for inclusion as predictor variables in multivariable models. The final model was chosen on the basis of those variables for which $p < 0.05$. In order to check that the resultant model fits sufficiently well, we performed model diagnostics, including the inclusion of all the relevant variables and the possibility of overfitting and multicollinearity. Specifically, possible overfitting was evaluated by comparing the fit of the complete model with that of reduced models (ie, removing predictors that did not influence the outcome variable). Regression results are reported as ORs and their respective 95% CIs. All statistical tests were two-tailed, and the significance level used was $p < 0.05$. The data were analyzed with the Stata Statistical Package V.12.0.

RESULTS

Study population

A total of 303 patients with a diagnosis of acute bronchiolitis were identified using ICD-10 codes, with 176 (58.1%) male subjects. The median (IQR) age was 3.0 (1.0–7.0) months, and the age group distribution was 203 (67.0%) less than 6 months, 92 (30.4%) between 6 and 12 months, and the remaining 8 (2.6%) between 13 and 24 months. The mean (SD) of the initial oxygen saturation was 88.0 (5.2) and the RSV was isolated in 115 of the total of 303 (38.0%) patients tested for the presence of RSV infection. All the demographic and clinical characteristics measured, according to the requirement or lack thereof for prolonged LOS for bronchiolitis, are presented in table 1.

Prolonged LOS for bronchiolitis

The median (IQR) of LOS for infants included in the study was 4.0 (3.0–5.0) days. The range of LOS was between 1 and 25 days. Among all 303 subjects, 36 (26.1%) were considered to have a prolonged LOS for bronchiolitis.

Predictors of prolonged LOS for bronchiolitis determined through multivariate analysis

As mentioned above, we adjusted logistic regression models to identify factors independently associated with prolonged LOS for bronchiolitis in the study population. We did not find evidence of overfitting when comparing the fit of the complete model presented here with that of reduced models (data not shown).

The predictive variables included in the complete model were age, gender, birth weight, occurrence of breast feeding for at least 6 months, number of days with respiratory symptoms, RSV isolation, the presence of apnea as an initial manifestation of bronchiolitis, initial oxygen saturation, and the presence of underlying disease conditions. We found that independent predictors of prolonged LOS for bronchiolitis in our study population included

age (OR 0.92; 95% CI 0.84 to 0.99; $p=0.049$), history of prematurity (OR 6.34; 95% CI 1.10 to 36.46; $p=0.038$), RSV isolation (OR 1.92; 95% CI 1.02 to 3.73; $p=0.048$), and initial oxygen saturation (OR 0.94; 95% CI 0.88 to 0.98; $p=0.048$) (table 2).

DISCUSSION

The results of this study show that in the Colombian inpatient population of patients with bronchiolitis studied, approximately a quarter underwent a prolonged LOS for observation and supportive therapy for their respiratory condition. Additionally, the results of the present study show that clinical variables such as age, history of prematurity, initial oxygen saturation, and RSV isolation independently predicted a prolonged LOS for bronchiolitis in the studied population.

The findings of the present study point to, as reported in high-income countries, the usefulness of clinical variables that may be objectively measured at admission or early in hospitalization for predicting prolonged LOS in infants suffering from bronchiolitis. While some of the identified predictors of prolonged LOS, such as age and initial oxygen saturation, cannot be modified, others, like gestational age at birth and RSV isolation, are potentially modifiable by effective interventions aimed at reducing premature birth and RSV transmission to young infants. Specifically, professional adherence to guidelines for preventing premature birth when possible and targeted education interventions directed toward parents/caregivers and healthcare providers that provide information on how to avoid RSV exposure and acquisition (including information that promotes hand-washing and hand hygiene measures²⁵ and breast feeding, and discourages exposure to environmental tobacco smoke,²⁶ overcrowding, and bedroom sharing²⁷) are potentially useful strategies that could help to reduce the LOS of patients with bronchiolitis.

Our findings are consistent with previous results reported in the literature and provide further evidence that younger infants and those born prematurely who are suffering from bronchiolitis are at a greater risk of requiring prolonged LOS. A retrospective study that included an inpatient population of 369 patients with bronchiolitis found that the age group 1–3 months was independently associated with an LOS ≥ 4 days.²⁸ Moler *et al*,²⁹ in a retrospective cohort study, examined an inpatient population of 802 infants with community-acquired RSV infection and reported findings similar to those of our study: nearly a quarter of the patients (23%) required a prolonged LOS, and prematurity was identified as an independent predictor of a prolonged LOS in the studied population. It is well known that young infants and those with history of premature birth are at a high risk for severe bronchiolitis and other adverse respiratory outcomes, mainly because of mechanical factors due to the smaller caliber of their airways (due to the fact that resistance is proportional to the inverse of the fourth power of the radius, the smaller the child, the greater the increase in the airway resistance, which is even further increased by the extensive inflammation and edema of the airways, increased mucus production, necrosis of airway epithelial cells, and the plugs composed of cellular debris and mucus in the bronchiole lumens that are characteristic of bronchiolitis),²⁹ but also because of immunologic factors (the function of all components of the innate immunity system, an early first line of defense that has a pivotal role in limiting the spread of respiratory viral infections within the lung, is weak in

newborns and especially in premature infants compared with later in life). This fact causes a tendency toward poor innate immune responses to viruses such as RSV, compared with later in life, making newborns and prematurely born infants more susceptible to viral infections and severe forms of these infections.³⁰³¹

With respect to initial oxygen saturation as an independent predictor of longer LOS for bronchiolitis, our findings agree well with previous studies, which have found that oxygen saturation and other severe disease markers at admission or early in hospitalization are predictive of longer LOS for the disease. Weisgerber *et al*⁴ reported several clinical markers identifiable on hospital day 2, such as minimum oxygen saturation, maximum respiratory rate, and clinical respiratory scores, as predictive of prolonged LOS in a population of 272 infants hospitalized for acute bronchiolitis. In the same manner, in a prospective cohort study that included 232 indigenous infants hospitalized with bronchiolitis, McCallum *et al*¹⁸ identified a 12-point severity score (including accessory muscle use) as the only factor associated with prolonged LOS. The presence of cyanosis was significantly associated with prolonged LOS in a population of 1046 children hospitalized for acute lower respiratory infections in a hospital located in Cairo, Egypt.³² Janahi *et al*²⁸ in a retrospective cohort study examined an inpatient population of 369 infants admitted with acute bronchiolitis in a hospital in Qatar, and found that retraction was an independent predictor of longer LOS. Finally, Mansbach *et al*³³ identified decreasing lowest oxygen saturation in the ED as a variable independently associated with ED LOS. However, although initial oxygen saturation could reflect a greater severity of the acute bronchiolitis episode, along with the subsequent prolonged LOS, the fact that hospitalizations of some infants with bronchiolitis are prolonged due to a perceived need for supplemental oxygen therapy based only on arbitrary thresholds of pulse oximetry readings has received increasing attention in studies and practice guidelines.³⁴ Therefore, further investigation into outcomes of different levels and durations of oxygen desaturation is warranted and would have the potential to reduce the LOS for bronchiolitis.³

Several studies have investigated whether severity of bronchiolitis is associated with specific viral infections, but the evidence is conflicting. While some studies have shown that lower respiratory infections produced by RSV have a more severe course compared with other viruses,³⁵³⁶ other studies have not confirmed this association.³²³⁷³⁸ A large, multicenter, multiyear prospective study of children hospitalized with bronchiolitis in 16 hospitals in the USA found that in comparison with children with RSV-only infections, those infected with RSV in combination with human rhino-virus (HRV) were more likely to have an LOS of 3 days or more and that those with HRV-only infections were less likely to present this outcome.³⁹ An observational study that included 369 patients admitted to the pediatric ward for bronchiolitis detected RSV in 51.2% of the cases and in second place HRV in 25.5% of cases, but found that identifying the viral agent did not influence disease severity or LOS.²⁸ In our study RSV isolation was associated with almost two times higher odds of prolonged LOS for bronchiolitis. However, we have to sound a note of caution with regard to such findings in our study for two reasons: First, we used a technique for the diagnosis of RSV infections that, in spite of being widely available, being easy to perform, and showing results in a short time, has reduced sensitivity and specificity, mainly in older children and adults.⁴⁰⁴¹ Second, in our study we did not test for viruses other than RSV. Notably, the use of such

a diagnostic technique may have caused a disease differential misclassification bias, which could have overestimated the true association between RSV isolation and the outcome variable. An additional factor that must be taken into account is that there is convincing evidence showing that children with a higher RSV genomic load have a higher risk for more severe bronchiolitis.³⁵⁴² However, we did not determine the RSV genomic load.

We are aware that our research may have at least three limitations. First, hospitalizations due to a number of medical conditions, including bronchiolitis, sometimes last longer than warranted by clinical factors alone (such as baseline severity of the disease, presence of comorbidities, and in-hospital complications) due to inefficiencies within the healthcare system, placement difficulties, operational delays, and payer-related issues. However, the plausibility of the identified clinical factors and their similarity to those identified in other previous studies suggest that the above-mentioned non-medical factors account for a minimal part of the causality of prolonged LOS in the studied population. Second, the study was conducted in a tertiary referral hospital, which could limit the generalization of the results to other settings. Finally, we did not include in the multivariate analyses some important predictors, such as other severe disease markers at admission (eg, a validated severity scoring instrument) and socioeconomic factors, and as is the case for other observational epidemiologic studies, residual confounding cannot be excluded, so interpretation of our results needs to be cautious.

In conclusion, the results of this study show that in the Colombian inpatient population of patients with bronchiolitis studied, approximately a quarter underwent a prolonged LOS for observation and supportive therapy for their respiratory condition. Additionally, clinical variables such as age, history of prematurity, initial oxygen saturation, and RSV isolation independently predicted prolonged LOS for bronchiolitis in the studied population.

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Significance of this study

What is already known about this subject?

- Bronchiolitis imposes a significant clinical and economic burden, particularly when patients require a prolonged length of stay (LOS).
- Bronchiolitis imposes a significant clinical and economic burden, particularly in low-income and middle-income countries (LMICs).
- Bronchiolitis burden is even greater when patients require a prolonged LOS.
- Despite its undoubted importance, prolonged LOS is an outcome measure that has received little attention in previous analyses of patients suffering from bronchiolitis.

What are the new findings?

- In an LMIC inpatient population of patients with bronchiolitis, approximately a quarter underwent a prolonged LOS for observation and supportive therapy for their respiratory condition.
- Clinical variables such as age, history of prematurity, initial oxygen saturation, and respiratory syncytial virus (RSV) isolation independently predicted a prolonged LOS for bronchiolitis in the studied population.
- Some of the identified predictors of prolonged LOS are potentially modifiable by effective interventions.

How might these results change the focus of research or clinical practice?

- Professional adherence to guidelines for preventing premature birth when possible and targeted education interventions directed toward parents/caregivers and healthcare providers that provide information on how to avoid RSV exposure and acquisition are potentially useful strategies that could help to reduce the LOS of patients with bronchiolitis.

Table 1

Clinicodemographic variables and underlying disease characteristics of otitis

Variable	Patients with prolonged hospitalizations for bronchiolitis (n=70)	Patients without prolonged hospitalizations for bronchiolitis (n=233)	p Values
Age, median (IQR)	2.0 (1.0–5.0)	4.0 (1.0–7.0)	0.003
Gender, male/female	46/24	130/103	0.140
Birth weight <2500 g	6 (8.6%)	29 (12.4%)	0.374
Breast feeding for at least 6 months	6 (8.6%)	39 (16.7%)	0.092
History of prematurity	8 (11.4%)	13 (5.6%)	0.853
History of bronchopulmonary dysplasia	3 (4.3%)	2 (0.9%)	0.048
Presence of other underlying disease conditions *	10 (14.3%)	29 (12.4%)	0.091
Number of days with respiratory symptoms			
Less than 24 hours	6 (8.6%)	25 (10.7%)	0.601
Between 24 and 48 hours	16 (22.9%)	55 (23.6%)	0.897
Between 48 and 72 hours	46 (65.7%)	146 (62.7%)	0.642
More than 72 hours	2 (2.9%)	2 (0.9%)	0.199
Apnea as an initial manifestation of bronchiolitis	3 (4.3%)	12 (5.2%)	0.770
Initial oxygen saturation, mean (SD)	86.4 (5.4)	88.4 (5.0)	0.012
Respiratory syncytial virus isolation	39 (55.7%)	76 (32.6%)	<0.001

Prolonged length of stay for bronchiolitis.

* Previous respiratory disease, congenital heart disease, and underlying neurologic disease.

Table 2

Predictors of prolonged hospitalization for bronchiolitis determined through multivariate analysis

Variable	OR (95% CI)	p Values
Age (months)	0.92 (0.84 to 0.99)	0.049
Male gender	1.10 (0.57 to 2.12)	0.765
Number of days with respiratory symptoms		
Less than 24 hours	1.00	–
Between 24 and 48 hours	1.30 (0.38 to 4.45)	0.672
Between 48 and 72 hours	1.17 (0.38 to 3.64)	0.774
More than 72 hours	7.38 (0.36 to 152.62)	0.196
Breast feeding less than 6 months	2.53 (0.82 to 7.77)	0.105
History of prematurity	6.34 (1.10 to 36.46)	0.038
History of bronchopulmonary dysplasia	12.54 (0.66 to 239.04)	0.093
Birth weight <2500 g	0.30 (0.07 to 1.32)	0.110
Apnea as an initial manifestation of bronchiolitis	0.22 (0.02 to 1.97)	0.175
Presence of other underlying disease conditions *	0.59 (0.14 to 2.56)	0.484
Initial oxygen saturation	0.94 (0.88 to 0.98)	0.048
Respiratory syncytial virus isolation	1.92 (1.02 to 3.73)	0.048

* Previous respiratory disease, congenital heart disease, and underlying neurologic disease.