BRIEF REPORT

Importance of respiratory syncytial virus as a predictor of hospital length of stay in bronchiolitis [version 1; peer review: 1 approved with reservations]

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Abstract

Introduction: Bronchiolitis is the leading cause of hospitalization in children. Estimate potentially preventable variables that impact the length of hospital stay are a priority to reduce the costs associated with this disease. This study aims to identify clinical variables associated with length of hospital stay of bronchiolitis in children in a tropical middle-income country

Methods: We conducted a retrospective cohort study in 417 infants with bronchiolitis in tertiary centers in Colombia. All medical records of all patients admitted to the emergency department were reviewed. To identify factors independently associated we use negative binomial regression model, to estimate incidence rate ratios (IRR) and adjust for potential confounding variables

Results: The median of the length of hospital stay was 3.68 days, with a range of 0.74 days to 29 days, 138 (33.17%) of patients have a hospital stay of 5 or more days. After modeling and controlling for potential confounders age <6 months, comorbidities (CHD or neurological), BPD, chest indrawing, RSV isolation, and C-reactive protein were independent predictors of LOS

Conclusions: Our results show that in infants with bronchiolitis, RSV isolation, age <6 months, comorbidities (CHD or neurological), BPD, chest indrawing, and C-reactive protein were independent predictors of LOS. As a potentially modifiable risk factor, efforts to reduce the probability of RSV infection can reduce the high medical cost associates with prolonged LOS in bronchiolitis.

Open Peer Review

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1. **Mauricio T. Caballero** , INFANT

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Any reports and responses or comments on the article can be found at the end of the article.

Keywords

Bronchiolitis, Colombia, respiratory syncytial virus, length of hospital stay, chest indrawing

This article is included in the **Pathogens** gateway.

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Introduction

Bronchiolitis is the most frequent lower respiratory tract infection in infants^{1,2}. One of the variables with more incidence in the financial burden of this disease is the hospital length of stay (LOS). Among inpatients with bronchiolitis, approximately a quarter undergo a prolonged length of stay (LOS)³. The high medical cost associated with prolonged LOS in bronchiolitis imposes an economic burden, especially in tropical middle-income countries⁴. LOS is a direct measure of the quality of health service⁵.

Some models have identified predictors of LOS such as age, underlying conditions (congenital heart disease, chronic lung conditions, immunocompromised states), low weight, male gender, clinical characteristics at admission, prematurity, RSV isolation⁶. However, many of these models lack accuracy⁷ or were made in patients without significant comorbidities⁸. Otherwise, in tropical areas in addition to genetic differences, the respiratory syncytial virus (RSV), generates differences in the burden of morbidity and mortality given the non-seasonality of these areas⁹. In this context, there is a critical need to explore predictors of LOS, especially in tropical areas, improving their accuracy of current models. This information will allow risk management for healthcare and prioritize care strategies in groups with a high probability of prolonged hospital stay to reduce their impact on hospital costs and morbidity. This study aims to identify clinical variables associated with LOS of bronchiolitis in children in a tropical middle-income country.

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. The municipality of Rionegro had a total population of 101,046 inhabitants, with two tertiary referral hospitals¹⁰. 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)¹¹. 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). Informed consent was obtained from all parents or caregivers of the patients included in the study, following the clinical research standards in Colombia, and prior approval by the ethics committee.

Procedures

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, exposure 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 bronchiolitis¹¹. Nasopharyngeal aspirate (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 not available in our institution consistently.

Statistical analysis

Continuous variables were presented as mean $\pm$ 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 length of hospital stay, we used a Poisson regression model, or negative binomial regression model in case of the presence of overdispersed count data, to estimate incidence rate ratios (IRR) and adjust for potential confounding variables. We only include initially variables associated with LOS with values of $p < 0.2$ or that change the effect estimate by more than 10% after their inclusion. The variable selection and modeling processes were made following the recommendations of Greenland¹². The goodness of fit of the model was evaluated using Hosmer–Lemeshow test and area under curve in Poisson regression or Akaike information criterion (AIC), Bayesian information criterion (BIC) in negative binomial regression. All statistical tests were two-tailed, and the significance level used was $p < 0.05$. The data were analyzed with Stata v15.0 (Stata Corporation, College Station, TX).

Results

Study population

During the study period, 417 cases of bronchiolitis were included. A total of 66% of the patient was less than 6 months, most of them males (60%), with supportive O₂ (83%). RSV was isolated in 200 patients (48%). Of these, 81 patients had a history of premature birth and 17 of them with BPD. A total of 20 patients had some cardiac or neurological disease and 10 of them with a history of use of palivizumab. Table 1 presents the clinical characteristics of the population. Deidentified individual-level raw data are available from Zenodo¹³.

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. Among all 417 patients, 138 (33.17%) have a hospital stay of 5 or more days

Multivariate analysis of predictors associated with LOS

Due to the significant presence of overdispersed count data was detected (Likelihood-ratio test of $\alpha=0$, $\chi^2=203.97$,

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

Variable	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)
Exclusive maternal breastfeeding for at least six month	102(24.4)
%SpO ₂ , median(ds)	89(0.28)
O ₂ supportive, n(%)	347(83.41)
Clinical & laboratory parameters	
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/mm ³)	51(12.26)
RSV positive	200(48.48)
Increased C-reactive protein (> 4 mg/lit.)	327(78.61)

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

CHD : Congenital heart disease, BPD: Bronchopulmonary dysplasia, RSV: Respiratory syncytial virus

p=0.000), a negative binomial regression model was used to adjust for potential confounding variables. The predictive variables included in the complete model were age, sex, premature birth, comorbidities, BPD, atopy, 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 negative binomial regression: age <6 months, comorbidities (CHD or neurological), BPD, chest indrawing, RSV isolation, and C-reactive protein were independent predictors of LOS (Table 2).

Discussion

The main purpose of this study was to determine the independent clinical variables associated with LOS of bronchiolitis in

children in tropical middle-income countries. Our study shows that RSV, age <6 months, comorbidities (CHD or neurological), BPD, chest indrawing, and C-reactive protein were independent predictors of LOS

Our results emphasize the importance of knowing the presence of RSV. While some predictors of LOS, such as age, comorbidities, and potentially initial signs of respiratory distress, can not be modified, others as RSV isolation are potentially modifiable by interventions such as futures vaccines or palivizumab in a high-risk population. Previous studies in populations with seasonality had revealed the importance of RSV as a predictor of hospital stay. 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

Table 2. Multivariate analysis of predictors associated with length of stay.

Variable	IRR	CI 95%	p
Age <6 months	0.998	0.998-0.999	0.000
Comorbidities (CHD or neurological)	2.119	1.459-3.078	0.000
Chest indrawing	1.322	1.115-1.567	0.001
BPD	1.610	1.087-2.385	0.017
RSV positive	1.593	1.346-1.886	0.000
C-reactive protein	1.005	1.002-1.008	0.006

load was an independent predictor of longer hospitalization. A 1-log higher RSV load predicted a 0.8-day longer hospitalization, reflects the higher RSV load that occur earlier in the disease¹⁴. Mansbach *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 prolonged LOS (>3 days) than patients with only HSV infection, but less than RSV+HRV co-infection (48% vs 28% vs 54%, $p < 0.001$ ¹⁵. 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)³. In Qatar, Janahi *et al.*, detected RSV in 51.2% of in 369 patients admitted to the pediatric ward for bronchiolitis, but no association was found between RSV and LOS¹⁶. Additionally, Masarweh *et al.*, in a retrospective study of 4793 infants with bronchiolitis in a single tertiary medical center in Israel between 2001–2009, found that RSV isolation did not correlate with LOS¹⁷. In this evidence, only the Mansbach study used the PCR assay for viral detection, but the results with immunofluorescence assay with respect to the predictive value of RSV were similar to the PCR assay. Indeed, the main problem of the studies mentioned above was the serious statistical mistakes of analyzing the LOS. While we used a negative binomial regression model, due to the presence of overdispersed count data, to adjust for potential confounding variables to analyze LOS, studies by Rodriguez, Devicenzo, and Mansbach dichotomize the LOS to perform logistic regression, while Masarweh's study performed a linear regression; being both approaches not completely correct. The loss of information from dichotomizing a continuous outcome is well documented in the literature, and even worse, analyzing a variable that does not have a normal distribution with a linear regression invalidates this method of analysis¹⁸. These pitfalls in statistical analysis can explain the lack of accuracy of predictive models⁶. The regression models recommended are median, gamma, or Poisson regression; which have some type I error but avoid the mistakes previously mentioned with the logistic or linear regression model.

Othe variable potentially modifiable associated with LOS was age <6 months. Our findings are consistent with previous results reported in the literature and provide further evidence that younger infants are at a greater risk of requiring prolonged LOS³. This can be explained because the smaller caliber of the airways in younger infants and poor innate immune response to RSV in newborns, making younger infants more susceptible to severe forms of viral infections and prolonged LOS^{19,20}. Preventive strategies such as the use of palivizumab in a high-risk population or the use of future vaccines that confer immunity in children under 6 months against RSV; will constitute possibly effective interventions in reducing the economic burden of this disease.

Several predictive models had reports consistently the chest indrawing as predictive of prolonged LOS that is which is biologically plausible and expected due that this sign also is a universal marker of severity of the disease, as well as the presence of underlying conditions (congenital heart disease, chronic lung conditions, immunocompromised states)^{3,6–8,21–23} or C-reactive protein (CRP) as a biomarker of severity and bacterial co-infection in patients hospitalized for bronchiolitis^{24–26}

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^{3,4}

Conclusion

Our results show that in infants with bronchiolitis, RSV, age <6 months, comorbidities (CHD or neurological), BPD, chest indrawing, and C-reactive protein were independent predictors of LOS in a tropical middle-income country. As a potentially

modifiable risk factor, efforts to reduce the probability of RSV infection can reduce the high medical cost associated with prolonged LOS in bronchiolitis.

Data availability

Underlying data

Zenodo: Importance of respiratory syncytial virus as a predictor of hospital length of stay in Bronchiolitis. <http://doi.org/10.5281/zenodo.4432434>¹³.

This project contains the raw data for each patient assessed in the present study.

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

Declarations

Ethics approval

The study protocol was reviewed and approved by the Institutional Review Board of Clínica Somer (No 281015) and the University of Antioquia (No 18/2015).

Consent for publication

All authors consent this paper for publication

Abbreviations

incidence rate ratios (IRR)

hospital length of stay (LOS)

respiratory syncytial virus (RSV)

Nasopharyngeal aspirate (NPA)

Bronchopulmonary dysplasia (BPD)

Chronic heart disease (CHD)

Authors' contributions

All the authors contributed in the same way from conception of the work to the publication of results. All Authors read and approved the manuscript.

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Mauricio T. Caballero

INFANT Foundation, Buenos Aires, Argentina

Importance of respiratory syncytial virus as a predictor of hospital length of stay in bronchiolitis is an interesting retrospective study conducted in tertiary centers in Rionegro, Colombia, from January 2019 to December 2019. The study explores variables associated with length of stay due to bronchiolitis in children under two years old. I have few comments regarding the study methods and results.

1. Respiratory syncytial virus was confirmed using direct immunofluorescence, which may underestimate the real burden of viral infection. How do authors estimate this could impact the results?
2. Authors did not mention if other respiratory viruses were explored and compared as associated to length of hospital stay.
3. Univariable analysis should be shown in an extra table.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Respiratory virus infection in children.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 30 Jun 2021

Jefferson Buendia, Universidad de Antioquia., Medellín, Colombia

We appreciate your valuable comments.

- *Respiratory syncytial virus was confirmed using direct immunofluorescence, which may underestimate the real burden of viral infection. How do authors estimate this could impact the results?*
- **Response:** Corrected. This limitation was added to the discussion of the paper.
- *Authors did not mention if other respiratory viruses were explored and compared as associated to length of hospital stay.*
- **Response:** Corrected. This limitation was added to the discussion of the paper.
- *Univariable analysis should be shown in an extra table.*
- **Response:** Corrected. Added a new table with the univariate analysis.

Competing Interests: None.

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