BRIEF REPORT

REVISED Importance of respiratory syncytial virus as a predictor of hospital length of stay in bronchiolitis [version 2; peer review: 1 approved with reservations]

Jefferson Antonio Buendia¹, Diana Guerrero Patino²

¹Pharmacology and Toxicology Department, Pharmacology and Toxicology Research Group, Faculty of Medicine, Universidad de Antioquia, Medellín, Antioquia, 053212, Colombia
²Hospital Infantil Concejo de Medellín, Medellín, Antioquia, 055420, Colombia

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.

Keywords
Bronchiolitis, Colombia, respiratory syncytial virus, length of hospital stay, chest indrawing
Corresponding author: Jefferson Antonio Buendia (jefferson.buendia@gmail.com)

Author roles: Buendia JA: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Guerrero Patino D: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2021 Buendia JA and Guerrero Patino D. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Buendia JA and Guerrero Patino D. Importance of respiratory syncytial virus as a predictor of hospital length of stay in bronchiolitis [version 2; peer review: 1 approved with reservations] F1000Research 2021, 10:110
https://doi.org/10.12688/f1000research.40670.2

First published: 15 Feb 2021, 10:110 https://doi.org/10.12688/f1000research.40670.1
Introduction
Bronchiolitis is the most frequent lower respiratory tract infection in infants\(^1\), 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)\(^2\). The high medical cost associates with prolonged LOS in bronchiolitis imposes an economic burden, especially in tropical middle-income countries\(^3\). LOS is a direct measure of the quality of health service\(^1\).

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 isolation\(^4\). However, many of these models lack accuracy or were made in patients without significant comorbidities\(^5\). 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 areas\(^6\). 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 hospitals\(^7\). 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)\(^8\). 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, %SpO\(_2\)), 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 bronchiolitis\(^9\). 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 no available in our institution consistently.

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 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 Greenland\(^10\). 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 month, most of them males (60%), with supportive \(O_2\) (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 Zenodo\(^11\).
Table 1. Demographic features and clinical information of the patients included in the study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age less than 6 month</td>
<td>277(66.43)</td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>251(60.34)</td>
</tr>
<tr>
<td>Premature birth</td>
<td>81(19.47)</td>
</tr>
<tr>
<td>Comorbidities (CHD or neurological)</td>
<td>20(4.81)</td>
</tr>
<tr>
<td>BPD</td>
<td>17(4.09)</td>
</tr>
<tr>
<td>Atopy</td>
<td>17(4.09)</td>
</tr>
<tr>
<td>Previously hospitalization by bronchiolitis</td>
<td>30(7.21)</td>
</tr>
<tr>
<td>Exposure to cigarette smoking</td>
<td>49(11.9)</td>
</tr>
<tr>
<td>Exclusive maternal breastfeeding for at least six month</td>
<td>102(24.4)</td>
</tr>
<tr>
<td>%SpO2, median(ds)</td>
<td>89(0.28)</td>
</tr>
<tr>
<td>O2 supportive, n(%)</td>
<td>347(83.41)</td>
</tr>
</tbody>
</table>

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/mm³): 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

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**

Univariate analysis is presented in Table 2. Due to the significant presence of overdispersed count data was detected (Likelihood-ratio test of alpha=0, \( \chi^2 = 203.97, p=0.000 \)), 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 3).

**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
Table 2. Demographic features and clinical information of the patients included in the study.

<table>
<thead>
<tr>
<th>Variable. n(%)</th>
<th>n (%)</th>
<th>Incidence rate-ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age less than 6 month</td>
<td>277(66.43)</td>
<td>0.998 (0.997-0.998)</td>
<td>0.000</td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>251(60.34)</td>
<td>0.048 (0.967-1.157)</td>
<td>0.218</td>
</tr>
<tr>
<td>Premature birth</td>
<td>81(19.47)</td>
<td>1.319 (1.191-1.461)</td>
<td>0.000</td>
</tr>
<tr>
<td>Comorbidities (CHD or neurological)</td>
<td>20(4.81)</td>
<td>1.787(1.525-2.094)</td>
<td>0.000</td>
</tr>
<tr>
<td>BPD</td>
<td>17(4.09)</td>
<td>1.037(0.835-1.289)</td>
<td>0.738</td>
</tr>
<tr>
<td>Atopy</td>
<td>17(4.09)</td>
<td>0.827(0.650-1.052)</td>
<td>0.123</td>
</tr>
<tr>
<td>Previously hospitalization by bronchiolitis</td>
<td>30(7.21)</td>
<td>0.750(0.619-0.908)</td>
<td>0.003</td>
</tr>
<tr>
<td>Exposure to cigarette smoking</td>
<td>49(11.9)</td>
<td>1.040(0.910-1.188)</td>
<td>0.563</td>
</tr>
<tr>
<td>Exclusive maternal breastfeeding for at least six month</td>
<td>102(24.4)</td>
<td>0.627(0.550-1.012)</td>
<td>0.423</td>
</tr>
<tr>
<td>SpO2, median(ds)</td>
<td>89(0.28)</td>
<td>1.007(0.999-1.015)</td>
<td>0.055</td>
</tr>
<tr>
<td>O2 supportive, n(%)</td>
<td>347(83.41)</td>
<td>2.227(1.899-2.611)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Clinical & laboratory parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
<th>Incidence rate-ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>119(28.61)</td>
<td>0.834(0.754-0.9232)</td>
<td>0.000</td>
</tr>
<tr>
<td>Chest indrawing</td>
<td>184(44.23)</td>
<td>1.416(1.297-1.545)</td>
<td>0.000</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>48(13.30)</td>
<td>1.181(1.028-1.357)</td>
<td>0.018</td>
</tr>
<tr>
<td>Rhonchi</td>
<td>137(32.93)</td>
<td>0.777(0.704-0.856)</td>
<td>0.000</td>
</tr>
<tr>
<td>Crepitation</td>
<td>137(32.93)</td>
<td>1.088(0.984-1.182)</td>
<td>0.160</td>
</tr>
<tr>
<td>Abnormal X-ray*</td>
<td>109(26.33)</td>
<td>1.055(0.957-1.164)</td>
<td>0.277</td>
</tr>
<tr>
<td>Leucocytosis (&gt; 15,000/mm3)</td>
<td>51(12.26)</td>
<td>1.179(1.040-1.337)</td>
<td>0.010</td>
</tr>
<tr>
<td>RSV positive</td>
<td>200(48.48)</td>
<td>1.653(1.511-1.807)</td>
<td>0.000</td>
</tr>
<tr>
<td>Increased C-reactive protein (&gt; 4 mg/lit.)</td>
<td>327(78.61)</td>
<td>0.849(0.767-0.940)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*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

Table 3. Multivariate analysis of predictors associated with length of stay.

<table>
<thead>
<tr>
<th></th>
<th>IRR</th>
<th>CI 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;6 months</td>
<td>0.998</td>
<td>0.998-0.999</td>
<td>0.000</td>
</tr>
<tr>
<td>Comorbidities (CHD or neurological)</td>
<td>2.119</td>
<td>1.459-3.078</td>
<td>0.000</td>
</tr>
<tr>
<td>Chest indrawing</td>
<td>1.322</td>
<td>1.115-1.567</td>
<td>0.001</td>
</tr>
<tr>
<td>BPD</td>
<td>1.610</td>
<td>1.087-2.385</td>
<td>0.017</td>
</tr>
<tr>
<td>RSV positive</td>
<td>1.593</td>
<td>1.346-1.886</td>
<td>0.000</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>1.005</td>
<td>1.002-1.008</td>
<td>0.006</td>
</tr>
</tbody>
</table>
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 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 disease. 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). Rodriguez-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). 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 LOS. 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 LOS. 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 analysis. These pitfalls in statistical analysis can explain the lack of accuracy of predictive models. The regression models recommended are median, gamma, or Poisson regression; which have some type 1 error but avoid the mistakes previously mentioned with the logistic or linear regression model.

The 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 LOS. 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. 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) or C-reactive protein (CRP) as a biomarker of severity and bacterial co-infection in patients hospitalized for bronchiolitis.

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, respiratory syncytial virus was confirmed using direct immunofluorescence, which may underestimate the real burden of viral infection. However, despite this possible underestimation, RSV infection was positively associated, and it is possible that the magnitude of the IRR is even greater. The detection of other respiratory viruses was not homogeneous in all patients, so to avoid information bias we decided not to include them in the analysis. We cannot rule out that other respiratory viruses have equal or greater association with our dependent variable in the study. Third, 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.

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 associates with prolonged LOS in bronchiolitis.

Data availability
Underlying data

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 Clinica Somer (No 281015) and the University of Antioquia (No 18/2015).

Page 6 of 9
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.

References
Open Peer Review

Current Peer Review Status: ?

Version 1

Reviewer Report 28 June 2021

https://doi.org/10.5256/f1000research.43735.r85075

© 2021 Caballero M. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com