Predictors of Severe Disease in a Hospitalized Population of Children With Acute Viral Lower Respiratory Tract Infections

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Although predictors of severe viral acute lower respiratory infections (ALRIs) in children have been reported, there have been few research studies performed in low- and middle-income countries (LMIC). The aim of the present study was to determine predictors of disease severity in a population of Colombian children <5 years of age with ALRI. In a prospective cohort study, we determined independent predictors of severe ALRI in a hospitalized population of children under 5 years old with ALRI during a 1-year period. We included both underlying disease conditions and the infecting respiratory viruses as predictor variables of severe disease. We defined severe disease as the necessity of pediatric intensive care unit admission. Of a total of 1,180 patients admitted with a diagnosis of ALRI, 416 (35.3%) were included because they were positive for any kind of respiratory virus. After controlling for potential confounders, it was found that a history of pulmonary hypertension (RR 3.62; CI 95% 2.38–5.52; \( P < 0.001 \)) and a history of recurrent wheezing (RR 1.77; CI 95% 1.12–2.79; \( P = 0.015 \)) were independent predictors of severe disease. The present study shows that respiratory viruses are significant causes of ALRI in infants and young children in Colombia, a typical tropical LMIC, especially during the rainy season. Additionally, the results of the present study show that clinical variables such as a history of pulmonary hypertension and a history of recurrent wheezing are more relevant for predicting ALRI severity than the infecting respiratory viruses.

KEY WORDS: acute respiratory infection; respiratory syncytial virus; pediatrics

INTRODUCTION

Viral acute lower respiratory infections (ALRIs) are important causes of morbidity and mortality, especially among children under 5 years of age [Costa et al., 2006]. Although ALRI poses a significant health problem in high-income countries, it is an even greater problem in low- and middle-income countries (LMIC). The problem is of such magnitude that ALRI is considered the leading cause of death among infants and children living in LMIC [Berman, 1991]. The clinical spectrum of disease varies from mild illness not requiring hospitalization to severe disease requiring assisted ventilation in the intensive care unit (ICU). Although the majority of ALRI affected children do not suffer from a condition severe enough to require significant intervention or hospitalization, a not insignificant proportion of children often require hospitalization for the treatment of their disease. In addition to the well-recognized and significant healthcare and clinical burden of ALRI, its economic burden is significant in terms of both direct medical costs and indirect costs for patients, for their families, and for healthcare systems, especially when patients require hospitalization [Paramore et al., 2004]. This clinical, health, and economic burden of ALRI is even greater when patients develop a severe disease, often requiring intensive medical interventions, prolonged hospitalizations, and
even assisted ventilation [Weisman, 2003]. Despite a lack of uniform criteria for considering an ALRI as severe, the most accepted criteria often include the rate and duration of hospitalization, ICU admission, oxygen requirement, and assisted ventilation. Identification of patients who are at a high risk for developing severe ALRI is important because these patients could benefit from preventive strategies such as lowering the threshold for admission to the hospital or optimizing the level of care or monitoring required for children who are admitted to the hospital [Rodriguez et al., 2014]. Although predictors of severe ALRI in children have been reported, such as young age, prematurity, underlying respiratory disease, congenital heart disease, cancer, lower socio-economic status, passive exposure to cigarette smoke, and the presence of viral coinfections, there have been few research studies performed in LMIC. Additionally, the majority of previous studies performed in LMIC have tested for only a limited number of respiratory viruses, mainly respiratory syncytial virus (RSV) and human adenovirus (HAdV) [Rodriguez et al., 2014; Rodriguez-Martinez et al., 2015]. Accordingly, there is still a considerable need for additional studies that establish predictors of severe ALRI in LMIC and test for additional respiratory viruses, not only because of its potential impact in the prevention of morbidity and mortality in children under 5 years of age but also because of the limited healthcare resources that typically are available in these countries.

The aim of the present single-center study was to determine predictors of disease severity in a hospitalized population of Colombian children <5 years of age with ALRI.

MATERIALS AND METHODS

Study Site

Bogota, the capital city of Colombia, contains one fifth of Colombia’s population. The city is located at an elevation of about 2,650 m (8,660 ft.) above sea level, and has an average annual temperature of 14.8˚C, varying between 1 and 26˚C, with an annual precipitation of about 672 mm. Two main seasonal variations in the city are the two dry seasons, running approximately from December to March and from June to August, and the two rainy seasons, running from March to May and from September to November. Although based on its per capita gross national income Colombia meets the World Bank criteria for classification as an upper middle income country, its poverty, income inequality, infant mortality rate, under-5 mortality rate, and other socioeconomic indicators look very much like those of a low-income country. [Morefield, 2015]. The Hospital Universitario Clinica San Rafael is a tertiary care university-based hospital located in the eastern central part of Bogota. The hospital has 320 beds and serves the city of Bogota (7,363,782 inhabitants) as well as other cities of the country.

Study Design and Procedures

A prospective cohort study was conducted during the period from January 2014 to January 2015 in a consecutive sample of patients aged <5 years hospitalized in the Hospital Universitario Clinica San Rafael with a diagnosis of ALRI. In our institution, patients with ALRI who are sick enough to be admitted to the hospital are tested for multiple viruses (RSV, HAdV, influenza, and parainfluenza) using an indirect immunofluorescence assay technique.

On the patients’ entry into the study, we collected the following demographic and clinical information: date of admission, age, gender, and the presence of underlying disease conditions such as prematurity, bronchopulmonary dysplasia (defined as oxygen dependence at 36 weeks of postmenstrual age), recurrent wheezing, congenital heart disease, malnutrition, and pulmonary hypertension. Likewise, prospectively we collected information related to outcomes of care or disease-severity parameters such as length of hospital stay, use of antibiotics, need for pediatric intensive care unit (PICU) admission, need for endotracheal intubation, and mortality. We defined severe disease as the necessity of PICU admission. In our institution, the following are the criteria for transferring children hospitalized due to ALRI to the PICU: worsening hypoxemia or hypercapnia, worsening respiratory distress, continuing requirement for more than 50% oxygen, hemodynamic instability, and/or apnea.

Respiratory Virus Detection

Nasopharyngeal aspirates (NPA) for respiratory virus detection were obtained from all participants on entry to the study or within 48 hr of admission for RSV, HAdV, influenza A & B, and parainfluenza 1, 2, & 3. Children were screened using an indirect immunofluorescence technique for identifying respiratory viruses in infected cell cultures (the Light Diagnostics™ Respiratory Panel Viral Screening and Identification IFA Kit). Samples for NPA were properly collected and transported before processing specimens. Specifically, NPA the specimen container was agitated to dislodge cells from the swab. For increased cell recovery, a few sterile glass beads were added to the specimen and vortexed or sonicated at 8–12 kc/sec for up to 1 min. The swab was discarded into sodium hypochlorite solution. Subsequently the specimen was centrifuged at 200–500g for 7–10 min, and the supernatant was used as inoculum material. Immediately prior to inoculation of specimens, cell cultures were examined for proper morphology. The monolayer was rinsed with fresh medium and aspirated. 0.2–0.5 ml of the inoculum was added to each of the culture vessels, in duplicate. After inoculation, the culture vessels were centrifuged for 30 min at 500–700g, and were let stand at 37˚C for 30 min. After the incubation period, the cultures were covered with a fresh maintenance medium and were incubated at 35–37˚C. The cell culture medium was...
renewed every 3–4 days. Cell cultures were examined daily for cytopathic effect. The mouse monoclonal antibodies provided with the diagnostic kit were bound to the appropriate viral antigen on the specimen slide. Unbound antibody was washed from the slide with phosphate buffered saline (PBS). This was followed by the addition of fluorescein isothiocyanate (FITC) labeled goat anti-mouse IgG which was bound to the antigen–antibody complex. FITC exhibited an apple green fluorescence when excited by ultraviolet light, allowing visualization of the complex by fluorescence microscopy. Cell fluorescence indicated a positive specimen.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range), whichever is appropriate. Categorical variables are presented 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 were analyzed using the Chi-square test or Fisher’s exact test, whichever was appropriate. To identify factors independently associated with severe ALRI, we used a Poisson regression with robust error variance. This regression technique allows for a conservative estimation of the relative risk when the outcome of interest occurs more than 10% of the time, as in the case of severe disease in the present analysis. [Zou, 2004]. The type of viral respiratory infection was included in the model as a dummy variable with a separate category for both RSV and HAdV, along with another category for additional viruses other than RSV and HAdV.

We compared multivariate models with and without interaction terms between recurrent wheezing and pulmonary hypertension, and between congenital heart disease and pulmonary hypertension, using likelihood ratio tests. Results of multivariate analyses are presented as relative risk (RR) with their respective 95% confidence intervals (CI). All statistical tests were two-tailed, and the significance level used was \( P < 0.05 \). The data were analyzed with the Statistical Package Stata 12.0 (Stata Corporation, College Station, TX).

RESULTS

Characteristics of the Study Population

From January 1st, 2014 to January 31st, 2015, a total of 1,180 patients were admitted with a diagnosis of ALRI, of whom 416 (35.3%) were selected for the present study because they were positive for some kind of respiratory virus. Of the 416 included patients, 212 (51.0%) were males, and the median (interquartile range [IQR]) age was 6.0 (3.0–14.0) months. The age group distribution was: 209 (50.2%) less than 6 months, 94 (22.6%) between 7 and 12 months, 76 (18.3%) between 13 and 24 months, and 37 (8.9%) between 25 and 36 months. Of the total of 416 patients included in the study, 86 (20.7%) were classified as having severe ALRI and the remaining 330 (79.3%) as having non-severe ALRI. Of the total of 416 patients, 352 (84.6%) had single RSV infections, 39 (9.4%) had single parainfluenza infections, seven (1.7%) had single influenza infections, and the remaining six (1.4%) had mixed respiratory infections. The median (IQR) of the length of hospital stay was 6.0 (4.0–10.0) days. With respect to the clinical diagnosis at admission, 147 (35.3%) patients were diagnosed as having bronchiolitis, 91 (21.9%) as having viral pneumonia, 51 (12.3%) as having viral and bacterial pneumonia, 20 (4.8%) as having bronchiolitis and bacterial pneumonia, and the remaining 75 (18.1%) received other diagnoses. Regarding comorbidities, it was found that 19 (4.6%) patients had pulmonary hypertension, 65 (15.6%) patients had a history of prematurity, 48 (11.5%) patients suffered from malnutrition, 43 (10.3%) patients had a history of recurrent wheezing, 31 (7.5%) patients had bronchopulmonary dysplasia, and 21 (5.0%) patients had a congenital heart disease. Out of the total of 19 patients with pulmonary hypertension, six (31.6%) had a history of congenital heart disease. Out of the total of 19 patients with pulmonary hypertension, five (26.3%) had a history of recurrent wheezing.

Monthly Distribution of Viral Respiratory Infections

Upon analyzing the data about monthly distribution of the viral respiratory infections, it was found that 261 (74.1%) RSV infections occurred during the 3-month period from March to May, the main rainy season in the country. Adenovirus was detected throughout the first semester of the year, with eight (66.7%) infections occurring during the 3-month period from March to May. Likewise, influenza A and parainfluenza III infections occurred mainly during the main rainy season in the country. Figure 1 shows the monthly number of viral respiratory infections, by type of identified virus.
Disease Severity and Mortality Data

With respect to severity of the respiratory disease, 86 (20.7%) patients were admitted to the PICU, and 67 (16.1%) patients required endotracheal intubation. None of the included patients died due to the respiratory infection. Regarding other parameters that reflect disease severity, out of the total of 416 patients included in the study, 165 (39.7%) had a mean length of hospital stay longer than 7 days, 163 (39.2%) were given antibiotics, and 24 (5.8%) required inotropic and or vasopressor support despite appropriate volume filling. In the bivariate analysis, children who were admitted to the PICU, compared to children who did not require PICU admission, were more likely to be male \((P = 0.048)\), to have a history of congenital heart disease \((P = 0.010)\), to have a history of recurrent wheezing \((P = 0.005)\), to have a history of pulmonary hypertension \((P < 0.001)\), and to have malnutrition as a comorbidity \((P = 0.002)\). Likewise, as expected, children who were admitted to the PICU, compared to children who did not require PICU admission, were more likely to have a mean length of hospital stay longer than 7 days, to require antibiotics, and to require inotropic and or vasopressor support despite appropriate volume filling \((P < 0.001)\). Interestingly, the age of the patients and the type of viral respiratory infection were not significantly associated with admission to the PICU in the bivariate analysis (Table I).

Predictors of Severe Viral Respiratory Infections Determined Through Multivariate Analysis

Multivariate analysis was conducted to determine factors associated with severe ALRI. The predictive variables included in the multivariate models were: age, gender, presence of comorbidities, and the type of the type of viral respiratory infection. After controlling for these potential confounders, it was found that a history of pulmonary hypertension \((RR 3.62; CI 95\% 2.38–5.52; P < 0.001)\) and having a history of recurrent wheezing \((RR 1.77; CI 95\% 1.12–2.79; P = 0.015)\) were independent predictors of severe disease in our sample of patients (Table II). After including the interaction terms, it was found that there was no interaction present regarding ALRI severity between recurrent wheezing and pulmonary hypertension \((P = 0.70)\), nor between congenital heart disease and pulmonary hypertension \((P = 0.30)\), so the interaction terms were excluded from the final model.

DISCUSSION

The present study shows that respiratory viruses are significant causes of ALRI in infants and young children in Colombia, a typical tropical LMIC, especially during the rainy season, which is defined as the 3-month period from March to May in the country. Additionally, the results of the present study show that clinical variables such as a history of pulmonary hypertension and a history of recurrent wheezing are more relevant for predicting ALRI severity than the infecting respiratory viruses.

We are confident that the present findings have gone some way towards enhancing our understanding of predictors of disease severity in young children with ALRI, and may have implications for planning interventions to try to reduce the huge burden of ALRI for young children living in Colombia and probably other similar LMIC. Specifically, children with the predictor clinical variables identified in the present study could benefit from specific management strategies such as education strategies for parents/caregivers on how to prevent respiratory viral infections, lowering the threshold for admission to the hospital for children with ALRI, or a more closely monitoring the care of patients.

**TABLE I.** Demographic Characteristics and Clinical Conditions of the Patients Included in the Study, According to Severity of Viral Acute Lower Respiratory Infections

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients needing PICU admission* ((n = 86))</th>
<th>Patients not needing PICU admission ((n = 330))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; median [interquartile range-IQR])</td>
<td>5.0 (3.0–10.0)</td>
<td>7.0 (3.0–14.0)</td>
<td>0.302</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>52/34</td>
<td>160/170</td>
<td>0.048</td>
</tr>
<tr>
<td>Prematurity</td>
<td>14 (16.3%)</td>
<td>51 (15.5%)</td>
<td>0.868</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>8 (9.5%)</td>
<td>23 (7.0%)</td>
<td>0.463</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>9 (10.5%)</td>
<td>12 (3.6%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Recurrent wheezing</td>
<td>16 (18.6%)</td>
<td>27 (8.2%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>16 (18.8%)</td>
<td>3 (0.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>18 (20.9%)</td>
<td>30 (9.1%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Use of antibiotics</td>
<td>67 (77.9%)</td>
<td>96 (29.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of hospital stay longer than 7 days</td>
<td>80 (99.0%)</td>
<td>85 (28.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inotropic and or vasopressor support</td>
<td>24 (27.9%)</td>
<td>0 (0%)</td>
<td>0.553</td>
</tr>
<tr>
<td>Type of viral respiratory infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>76 (88.4%)</td>
<td>276 (83.6%)</td>
<td></td>
</tr>
<tr>
<td>Human adenovirus</td>
<td>2 (2.3%)</td>
<td>10 (3.0%)</td>
<td></td>
</tr>
<tr>
<td>Other viruses</td>
<td>8 (9.3%)</td>
<td>44 (13.3%)</td>
<td></td>
</tr>
</tbody>
</table>

*PICU, pediatric intensive care unit.

Bold values signify \((P\)-value <0.05)
The findings of the present study are consistent with previous findings in the literature regarding risk factors for severe ALRI in young children. Ricart et al. [2013] assessed whether classical clinical risk factors are more important than the respiratory viruses involved in the infection for determining the severity of ALRI in young children. In the multivariate analysis of their study that included the infecting viruses and clinical variables, they found that while bronchopulmonary dysplasia, congenital heart disease, prematurity, and fever were independent predictors of severe ALRI, the viruses involved in the infection were not independently associated with severe disease [Ricart et al., 2013]. The findings with respect to pulmonary hypertension as an independent predictor of severe ALRI are consistent with other studies in which cardiopulmonary conditions have been shown to predict severe cases of ALRI. MacDonald et al. [1982] prospectively studied 699 infants hospitalized for ALRI and found that RSV infected infants with congenital heart disease had significantly more severe disease than those without congenital heart disease as judged by the requirement for intensive care and assisted ventilation and by the mortality rate. They also found that pulmonary hypertension was the one condition particularly associated with severe respiratory disease [MacDonald et al., 1982]. Navas et al. [1992] studied the outcomes in 1,584 children at high risk for death or complications from respiratory disease who were hospitalized with RSV-ALRI. As in our study, the authors also found a low mortality rate (1%) and a higher rate of PICU transfer in patients with pulmonary hypertension compared with all other groups [Navas et al., 1992]. Likewise, Moler et al. [1992], in a retrospective cohort study, determined the morbidity and mortality rates of pediatric patients hospitalized for RSV-ALRI. Out of the total of the 740 patients included in the study, 79 had congenital heart disease, and 40 of these patients had pulmonary hypertension. The authors found that when examining only patients with congenital heart disease, those patients with pulmonary hypertension had increased hospital stays and greater intensive care and mechanical ventilation durations compared with patients without this diagnosis. They concluded that RSV-ALRI in congenital heart disease patients with pulmonary hypertension is associated with increased morbidity but not increased mortality rates [Moler et al., 1992]. Although association between severe RSV-ALRI and pulmonary hypertension coexisting with congenital heart disease has been noted previously, we also found this association in ALRI caused by other respiratory viruses and in patients with pulmonary hypertension not necessarily coexisting with congenital heart disease. The pathophysiology of the increase in ALRI severity in patients with pulmonary hypertension is not clear. It has been speculated that patients with congenital heart disease associated with pulmonary hypertension are less able to compensate for the altered distribution of ventilation that occurs with ALRIIs [MacDonald et al., 1982]. Likewise, it has been reported that pulmonary hypertension per se can be associated with hypoxemia, which can be partly related to ventilation/perfusion mismatch, low diffusion capacity, low cardiac output, and/or right-to-left shunting [Vodoz et al., 2009]. However, it is important to note that some previously healthy patients with acute ALRIIs develop elevated pulmonary artery pressures, and pulmonary hypertension can be considered a criterion for establishing the severity of an acute ALRI episode [Bardi-Peti and Ciofu, 2010]. The latter is not the case for patients included in our study, because all patients had already been diagnosed with pulmonary hypertension before the episode of severe ALRI.

With regard to the finding of a history of recurrent wheezing as a predictor severe ALRI, it is unclear whether children who are predisposed to recurrent wheezing/asthma are more prone to be infected with respiratory viruses or whether they are more likely to have severe disease when infected with respiratory viruses. Anyway, the American Academy of
Pediátricas guideline for treatment of bronchiolitis recommends identifying a history of underlying conditions that may be associated with an increased risk of progression to severe disease, among which the occurrence of previous episodes of wheezing is included [Ralston et al., 2014]. Likewise, it has been reported that children with a history of wheezing/asthma have more severe rhinovirus-ALRI than those without such a history when the rate of hospitalization is the criterion for establishing the ALRI severity [Miller et al., 2007]. In contrast to our previous findings showing that age less than 6 months, prematurity, congenital heart disease, and mixed RSV-adenovirus infection were independent predictors of severe ALRI in a different population of patients, [Rodriguez et al., 2014] the present study identified different predictors of severe ALRI. Possible explanations for these discrepancies might be differences in environmental, host (e.g., genetic immune response, previous immune condition, infected target cells), and viral factors (e.g., serotypes) [Barberi et al., 2012].

We are aware that our research may have three limitations. The first is that not all included patients were screened for the presence of pulmonary hypertension. We assumed that patients never diagnosed with pulmonary hypertension did not have the disease. The nonspecific nature of the presenting symptoms and signs of pulmonary hypertension, especially in the early stage of the disease, can lead to a differential misclassification bias due to the error in the pulmonary hypertension diagnosis, where the RR is specifically biased upward. Although a differential misclassification bias cannot be excluded, we consider it unlikely that its magnitude could account for our findings. The second is that 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 analyses some important predictors such as birth weight and parental smoking, and as is the case for other observational epidemiologic studies, residual confounding cannot be excluded, so interpretation of our results needs to be cautious. The main strength of this study is that we included both underlying disease conditions and the infecting respiratory viruses (including additional viruses other than RSV and HAdV) as predictor variables of severe ALRI.

In conclusion, the present study shows that in Colombia, a typical tropical LMIC, respiratory viruses are significant causes of ALRI in infants and young children, especially during the rainy season. Additionally, clinical variables such as a history of pulmonary hypertension and a history of recurrent wheezing are more relevant in predicting ALRI severity than the infecting respiratory viruses. The identified predictors of severe ALRI should be taken into account when planning interventions, in order to reduce the burden of ALRI in young children living in these regions.

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