

นิพนธ์ต้นฉบับ

Original Article

ลักษณะทางคลินิกและปัจจัยที่สัมพันธ์กับความรุนแรงของโรคติดเชื้อทางเดินหายใจส่วนล่างจากเชื้อไวรัสอาร์เอสวีในผู้ป่วยเด็ก โรงพยาบาลเจ้าพระยาอภัยมราช

Clinical Characteristics and Factors Associated with Severity of Lower Respiratory Tract Infection from Respiratory Syncytial Virus (RSV) in Pediatric Patients at Chaoprayayommarat Hospital

ธัญญกร นันทียกุล

โรงพยาบาลเจ้าพระยาอภัยมราช
จังหวัดสุพรรณบุรี

Thunyakorn Nuntiyagul

Chaoprayayommarat Hospital

Suphan Buri province

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บทคัดย่อ

การติดเชื้อทางเดินหายใจส่วนล่างจากเชื้ออาร์เอสวี เป็นสาเหตุสำคัญของการนอนโรงพยาบาลในเด็ก การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาลักษณะทางคลินิก ปัจจัยที่สัมพันธ์กับความรุนแรงของโรคติดเชื้อทางเดินหายใจส่วนล่างจากอาร์เอสวีในเด็ก และการเกิดเสียงหวีดซ้ำหลังจากเคยติดเชื้ออาร์เอสวีนาน 1 ปี การศึกษานี้เป็นการศึกษาเชิงวิเคราะห์ข้อมูลย้อนหลังแบบตัดขวาง วิเคราะห์ข้อมูลจากเวชระเบียนผู้ป่วยเด็กอายุ 0-6 ปี เป็นโรคติดเชื้อทางเดินหายใจส่วนล่างจากอาร์เอสวี โดยเก็บสิ่งส่งตรวจจากโพรงจมูก ตรวจด้วยวิธีการทดสอบหาแอนติเจนของไวรัสอาร์เอสวีอย่างรวดเร็ว และรับการรักษาในโรงพยาบาล ตั้งแต่เดือนตุลาคมถึงธันวาคม พ.ศ. 2563 แบ่งผู้ป่วยออกเป็น 2 กลุ่ม คือ กลุ่มอาการรุนแรง (ปอดอักเสบและหลอดลมฝอยอักเสบ) และกลุ่มอาการไม่รุนแรง (หลอดลมอักเสบ) ใช้การวิเคราะห์ถดถอยลอจิสติกพหุคูณ หาปัจจัยที่สัมพันธ์กับอาการรุนแรง ผลการศึกษาพบว่าผู้ป่วยเด็กติดเชื้อทางเดินหายใจส่วนล่างจากอาร์เอสวี 157 ราย ผู้ป่วยเป็นปอดอักเสบและหลอดลมฝอยอักเสบ 102 ราย (ร้อยละ 65) ผู้ป่วยเป็นหลอดลมอักเสบ 55 ราย (ร้อยละ 35) พบเด็กอายุน้อยกว่า 6 เดือนที่ติดเชื้ออาร์เอสวีมีโอกาสเกิดอาการรุนแรงมากกว่าเด็กอายุ 1-6 ปี 18.6 เท่า ($OR_{adj} 18.6, 95\%CI 2.37-145.71, p=0.005$) และ ฟังปอดมีเสียงหวีดสัมพันธ์กับความรุนแรงของโรคติดเชื้ออาร์เอสวี 4.5 เท่า ($OR_{adj} 4.5, 95\%CI 1.68-11.93, p=0.003$) การศึกษานี้สรุปได้ว่า เด็กอายุน้อยกว่า 6 เดือน ฟังปอดมีเสียงหวีดสัมพันธ์กับความรุนแรงของโรคติดเชื้อทางเดินหายใจส่วนล่างจากอาร์เอสวี

ติดต่อผู้พิมพ์: ธัญญกร นันทียกุล

อีเมล : thunyakorn.n2515@gmail.com

Abstract

The lower respiratory tract infection (LRTI) caused by the respiratory syncytial virus (RSV) is a leading cause of hospitalization in children. This study aimed to determine clinical characteristics and factors associated with the severity of LRTI from RSV in children and recurrent wheezing at one year after RSV infection. This retrospective analytic cross-sectional study was conducted by reviewing the medical records of pediatric patients aged 0 to 6 years who have been diagnosed with LRTI from RSV. Specimens were collected from nasal cavity and tested using a rapid antigen detection test for RSV. These pediatric patients were admitted to the pediatrics department between October and December 2020. The patients were categorized into two groups: the severe group with pneumonia and bronchiolitis; and the non-severe group with bronchitis. Multiple logistic regression analysis was used to determine the factors associated with severity. The study found that, of the 157 children with LRTI from RSV, 102 (65%) had pneumonia and bronchiolitis, whereas 55 (35%) had bronchitis. Children aged below 6 months with RSV infection were 18.6 times more likely to develop severe disease than children aged 1–6 years (OR_{adj} 18.6, 95% CI 2.37–145.71, $p=0.005$) and abnormal lung auscultation of wheezing was associated with the severity of RSV equal to 4.5 times (OR_{adj} 4.5, 95% CI 1.68–11.93, $p=0.003$). This study demonstrated that children below 6 months old and those who had clinical pulmonary signs of wheezing were associated with the severity of LRTI from RSV.

Correspondence: Thunyakorn Nuntiyagul

E-mail: thunyakorn.n2515@gmail.com

คำสำคัญ

ปัจจัยที่สัมพันธ์กับความรุนแรง, ปอดอักเสบ, หลอดลมฝอยอักเสบ, อาร์เอสวี

Keywords

Factors associated with severity, Pneumonia, Bronchiolitis, RSV

Introduction

RSV virus was first found in chimpanzees. It was later discovered that it can cause infections in the lower respiratory tract (LRT) and bronchioles in humans. This illness can be found all over the world. Among the LRTI, it most commonly leads to bronchiolitis and, subsequently, pneumonia. Severe symptoms, particularly in infants under 6 months of age and with respiratory or heart problems, nerve and muscle system diseases, immune deficiencies, bronchopulmonary dysplasia as well as premature babies.⁽¹⁾ Currently, there is no effective and safe medication

or vaccine for RSV infections, and infection with this virus continues to be a clinical problem worldwide.⁽¹⁾ Most RSV-infected infants experience upper respiratory tract symptoms, and 20% to 30% develop LRT disease such as bronchiolitis and/or pneumonia with their first infection.⁽²⁾ Previous research revealed that RSV was the leading cause of death in younger infants (aged 28 days to < six months of age), accounted for half of all deaths attributed to RSV (12 of 24 [50%]), and RSV was determined to have caused 6.5% of all deaths in this age group.⁽³⁾ In addition, LRTI from RSV is also a major cause of community mortality in

developing countries.⁽⁴⁾ According to statistical data, the most common cause of pediatric in-patients at Chaoprayayommarat Hospital was respiratory tract infection. There was an outbreak of RSV in pediatric patients in several provinces, including Suphan Buri, from October to December 2020. Some parents were concerned about the disease's severity. In addition, there were previous studies both domestically⁽⁵⁻⁶⁾ and internationally⁽⁷⁻⁹⁾ to identify the main risk factors associated with the severity of RSV infection in the LRT in pediatric patients. These studies' findings were different. Besides, RSV-associated bronchiolitis might be associated with multiple wheezing and abnormalities in lung function.⁽¹⁻²⁾

Therefore, the investigator was interested in studying the clinical characteristics, and factors associated with the severity of LRTI from RSV and recurrent wheezing after RSV infection for one year in pediatric patients at Chaoprayayommarat Hospital. The result of this study will be the baseline data of the hospital.

Materials & Methods

Study design

This retrospective analytic cross-sectional study was conducted at Chaoprayayommarat Hospital, Thailand. It was approved by the Research Ethical Committee of Chaoprayayommarat Hospital (YM017/2564) and registered in the Thai Clinical Trial Registry (TCTR20220129002). The medical records of pediatric patients with RSV-infected aged 0-6 years who were admitted between October 1, 2020 and December 31, 2020 were retrospectively reviewed. The patients were followed up every 6 months until one year after RSV infection by telephone to their parents to inquire the episode of wheezing

symptoms, dyspnea, and need for bronchodilators (oral and/or nebulization). The study enrolled 157 children and performed nasal cavity swab tests with the rapid antigen detection test (immunochromatographic tests) to confirm RSV infection. The exclusion criteria were patients who refused treatment and incomplete medical records. All of the pediatric patients had fever, cough, rapid breathing, or dyspnea, and also abnormal lung sounds. Abnormal CXR findings determined by the pediatrician and/or radiologist were the main criteria to diagnose and divide patients into acute bronchitis, bronchopneumonia, and bronchiolitis in this study. Acute bronchitis, radiographic evidence of peribronchovascular thickening. Bronchopneumonia, radiographic evidence of perihilar peribronchovascular interstitial infiltration and consolidation. Acute bronchiolitis, radiographic evidence of peribronchovascular thickening, interstitial infiltration, flattened diaphragm, hyperinflation and often atelectasis.⁽¹⁰⁾ Wheezes are high-pitched, soft musical sounds produced by the breath as it rapidly passes through the narrowing airway, which indicate lower airway obstruction.⁽¹⁰⁾

The RSV-infected children were admitted by the pediatrician for treatment based on hospitalization criteria such as dyspnea, retraction of the chest wall or tachypnea with a faster than normal breathing rate according to the World Health Organization's criteria for age⁽¹¹⁾, hypoxia or having oxygen saturation of less than 95%, respiratory failure, shock, dehydration or poor appetite. Then taking a history and performing a physical examination. The demographic data included age, sex, underlying disease, history of birth, birth weight, family smoking, parents with asthma or allergy, clinical signs and symptoms, body temperature, blood oxygen saturation, respiratory rate, abnormal lung sound, admitted at PICU and chest X-rays were

recorded. The patients were categorized into two groups; group 1 (severe group): bronchopneumonia and bronchiolitis; and group 2 (non-severe group): bronchitis, as shown in figure 1. All patients received standard treatment.⁽¹⁰⁾ After hospital discharge, the patients were followed up every 6 months until one year by telephone to their parents to inquire about the episode of wheezing symptoms, dyspnea, and need for bronchodilators (oral and/or nebulization). In addition, the medical records of these children who came to the hospital one year after RSV infection for dyspnea were also reviewed.

The predictor variables were age, sex, underlying disease, history of birth, birth weight, family smoking, parents with asthma /allergy, symptoms, respiratory rate, abnormal lung sound of wheezing.

Sample size calculation: A sample size calculation was performed with the aim of determining the associated factors with the severe group. The number of predictor variables in this study was 10 from review literatures.^(1-2,5-7,12) The ratio of sample size to predictor variables should be 15:1⁽¹³⁾ in multiple logistic regression. So the sample size was at least 150. Thus, with the enrollment of study pediatric patients and complete data collection, the

sample size of this study was 157.

Statistical analysis

The categorical data were presented as number (n) and percentage (%), and analyzed using Chi-square or Fisher's exact test for association with severity. A univariate logistic regression analysis was performed (reported as crude OR) to investigate the association of the relevant predictor variables. The dichotomous variable "severity" (severe/non severe) was used as a target criterion. All predictor variables met the conditions for multiple logistic regression analysis⁽¹⁴⁾, and they were further assessed with multiple logistic regression analysis by using the enter method. Factor associated with severity on univariate analysis (p -value<0.2) and no multicollinearity (variance inflation factor (VIF) below 4 and tolerance greater than 0.2) were included into the full model. The reduced model was done by excluded the variables which were not statistically significant association (p >0.05). The results were reported as crude and adjusted OR with 95% confidence interval (CI) to illustrate the significant factors associated with severity and p -value<0.05 was considered to be statistically significant. All were analyzed by SPSS version 20.0.

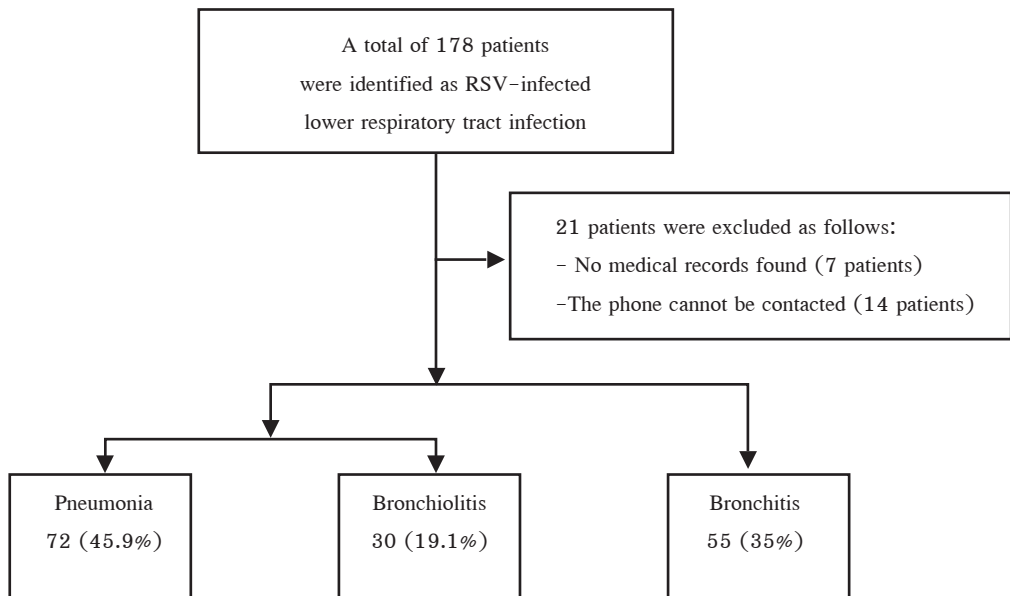


Figure 1 Flow diagram showing the enrollment of study pediatric patients.

Results

The demographic data of children with LRTI from RSV is shown in Table 1. From this study, of the 157 children with RSV infection, the severe group: 102 (65%) were pneumonia and bronchiolitis, whereas in the non-severe group, 55 (35%) were

bronchitis. Among the severe group, 72 (45.9%) were pneumonia and 30 (19.1%) were bronchiolitis. In the age groups of 0-<6 months and 6 months-<1 year, pneumonia and bronchiolitis were statistically significantly more common than in the age group of 1-6 years ($p<0.001$) (Table 1).

Table 1 Demographic data of patients with LRTI from RSV

Variables	(Severe group) Pneumonia and Bronchiolitis (n=102)	(Non-severe Group) Bronchitis (n=55)	p-value
Age (n, %)			<0.001 ^{a,b}
0-<6 months	24 (23.5)	1 (1.8)	
6 months-<1 year	15 (14.7)	4 (7.3)	
1-6 years	63 (61.8)	50 (90.9)	
Sex (n, %)			0.065 ^a
Male	62 (60.8)	25 (45.5)	
Female	40 (39.2)	30 (54.5)	

Table 1 Demographic data of patients with LRTI from RSV (continue)

Variables	(Severe group) Pneumonia and Bronchiolitis (n=102)	(Non-severe Group) Bronchitis (n=55)	p-value
Underlying disease (n, %)			
No underlying disease	84 (82.4)	43 (78.2)	0.526 ^a
Asthma	5 (4.9)	4 (7.3)	0.721 ^b
Allergic rhinitis	2 (2.0)	2 (3.6)	0.612 ^b
Congenital heart disease	3 (2.9)	0 (0.0)	0.552 ^b
Neuromuscular disease	0 (0.0)	1 (1.8)	0.35 ^b
Chronic lung disease	1 (1.0)	0 (0.0)	1.00 ^b
Others	7 (6.9)	5 (9.1)	0.754 ^b
History of birth (n, %)			0.886 ^b
Term ≥37 weeks	94 (92.2)	52 (94.5)	
Preterm 35–37 weeks	4 (3.9)	2 (3.6)	
Preterm <35 weeks	4 (3.9)	1 (1.8)	
Birth weight (n, %)			1.00 ^b
<2,500 gram	8 (7.8)	4 (7.3)	
≥2,500 gram	94 (92.2)	51 (92.7)	
Family smoking (n, %)	40 (39.2)	30 (54.5)	0.065 ^a
Parents with asthma/allergy (n, %)	34 (33.3)	14 (25.5)	0.307 ^a

* $p < 0.05$ indicating statistical significance, a = Chi-square test, b = Fisher's Exact test

The most common symptoms of RSV-infected pneumonia and bronchiolitis were cough (100%), rhinorrhea/nasal congestion (98%), and fever (93.1%), respectively. Among patients with bronchitis, cough (100%) was the most common symptom, followed by fever (98.2%) and rhinorrhea/nasal congestion (98.2%). The group with pneumonia and bronchiolitis had more tachypnea and dyspnea symptoms than the group with bronchitis ($p < 0.001$). Physical examination results showed a lower blood

oxygen saturation value ($< 95\%$) and a respiratory rate of at least 40 breaths per minute in the severe group than in the non-severe group ($p = 0.001$, $p < 0.001$). In addition, abnormal lung auscultation, wheezing, and crepitation were more common in pneumonia and bronchiolitis than in bronchitis ($p < 0.001$, $p < 0.001$). Patients with pneumonia and bronchiolitis require PICU more frequently ($p = 0.004$) than those with bronchitis (Table 2). All pediatric patients survived.

Table 2 Clinical signs and symptoms of patients with LRTI from RSV

Variables	Pneumonia and Bronchiolitis (n=102)	Bronchitis (n=55)	p-value
Symptoms[†] (n, %)			
Fever	95 (93.1)	54 (98.2)	0.262 ^b
Cough	102 (100)	55 (100)	N/A
Rhinorrhea /nasal congestion	100 (98.0)	54 (98.2)	1.00 ^b
Vomiting	26 (25.5)	18 (32.7)	0.335 ^a
Diarrhea	17 (16.7)	5 (9.1)	0.192 ^a
Tachypnea/dyspnea	77 (75.5)	16 (29.1)	<0.001 ^{*,a}
Cyanosis	6 (5.9)	0 (0.0)	0.092 ^b
Apnea/respiratory failure	4 (3.9)	0 (0.0)	0.298 ^b
Physical examination			
Highest body temperature (n,%)			0.342 ^a
≥39 °C	21 (20.6)	15 (27.3)	
<39 °C	81 (79.4)	40 (72.7)	
Lowest oxygen saturation (n, %)			0.001 ^{*,b}
<95%	19 (18.6)	0 (0.0)	
>95%	83 (81.4)	55 (100)	
Respiratory rate (n, %)			<0.001 ^{*,a}
<40 /min	49 (48.0)	45 (81.8)	
40–60 /min	46 (45.1)	10 (18.2)	
>60 /min	7 (6.9)	0 (0.0)	
Abnormal lung sound (n, %)			
rhonchi	100 (98.0)	52 (94.5)	0.344 ^b
wheezing	40 (39.2)	6 (10.9)	<0.001 ^{*,a}
crepitation	58 (56.9)	6 (10.9)	<0.001 ^{*,a}
Admitted at PICU	13 (12.7)	0 (0.00)	0.004 ^{*,b}

[†]One patient may had more than one symptom, * $p < 0.05$ indicating statistical significance, a = Chi-square test, b = Fisher's Exact test, N/A=not applicable.

Among the predictor variables, there was no multicollinearity between them. The collinearity statistics: the VIF values for age (1.07), sex (1.04), wheezing (1.04) and family smoking (1.01) were lower than 4. The tolerance values for age (0.94), sex (0.96), wheezing (0.96) and family smoking (0.99) were greater than 0.2. Based on multiple logistic regression analysis (enter method), the severity of RSV in children aged 0–< 6 months was

18.6 times greater than in children aged 1–6 years (OR_{adj} 18.6, 95% CI 2.37–145.71, $p=0.005$) and abnormal lung auscultation of wheezing was associated with the severity of RSV equal to 4.5 times (O_{Radj} 4.5, 95% CI 1.68–11.93, $p=0.003$) (Table 3). When following-up pediatric patients after discharge for one year, the severe group had significantly more consequences for any wheezing than the non-severe group ($p=0.04$) (Table 4).

Table 3 Univariate and multiple logistic regression analysis of clinical factors associated with severity of LRTI from RSV

Variables	Crude OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age						
1–6 years	1	reference		1	reference	
6 months<1 year	2.98	0.93–9.53	0.066	2.35	0.68–8.15	0.18
0–<6 months	19.05	2.5–145.69	0.005*	18.57	2.37–145.71	0.005*
Sex						
Female	1	reference				
Male	1.86	0.96–3.61	0.07			
wheezing						
no	1	reference		1	reference	
yes	5.27	2.07–13.44	0.001*	4.48	1.68–11.93	0.003*
Family smoking						
no	1	reference				
yes	0.54	0.28–1.04	0.07			

* $p < 0.05$ indicating statistical significance**Table 4** Number of followed-up pediatric patients who had episodes of any wheezing for one year after RSV infection

Variables	Pneumonia and bronchiolitis n=102	Bronchitis n =55	p-value
any wheezing (n, %)			0.04 ^{*,a}
no	82 (80.4)	51 (92.7)	
yes	20 (19.6)	4 (7.3)	

* $p < 0.05$ indicating statistical significance, a = Chi-square test.

Discussion

In this study, the group of severe LRTI from RSV mainly had pneumonia (45.9%) and bronchiolitis (19.1%), similar to a study by Srihareonvijit C that found that the RSV– hospitalization among children was pneumonia (46.5%) and bronchiolitis (20.5%).⁽¹²⁾ Children who had tachypnea or dyspnea had statistically significantly more severe symptoms, similarly to other studies.⁽¹²⁾ A physical examination revealed a respiratory rate of more than 60 breaths per minute, and a blood oxygen saturation value below 95% indicates the severity of the disease.^(12,15) In addition, abnormal lung

auscultation with crepitation and wheezing, indicates a LRTI⁽¹⁰⁾, which often requires bronchodilators, nebulized hypertonic saline, intravenous fluid, sputum drainage, and supplemental oxygenation to correct hypoxia, as appropriately.^(10,15) In cases of acute respiratory failure, mechanical ventilation was necessary.⁽¹⁰⁾ According to the findings of this study, the severe group requires more supplemental oxygen and admission to the PICU than the non–severe group.

The severity of RSV in children aged 0–< 6 months was 18.6 times greater than in children aged 1–6 years. Similarly, a study by Simoes EAF found

that age <6 months is a significant risk factors for severe RSV LRTI.⁽¹⁶⁾ Several factors play an important role, including the immature immune system, bronchial narrowing, excessive aeration, disruption in gas exchange occur as a result of infiltration of the airway by inflammatory cells, necrosis in the respiratory tract epithelium, shedding of necrotic cells, excessive mucus production, decreased ciliary function, airway edema, and a bias toward a T helper type 2 response, which is related to the disease severity.^(1,17-18) In addition, abnormal lung auscultation of wheezing was associated with the severity of RSV equal to 4.5 times as similar to other studies.^(12,19) A study by Ueno F et al found that having decreased breath sounds (OR_{adj} : 8.6), wheezing (OR_{adj} : 3.1), rales (OR_{adj} : 6.2), alar flaring (OR_{adj} : 26.7), axillary temperature $\geq 38^{\circ}C$ (OR_{adj} : 2.0) and tachycardia (OR_{adj} : 2.0) were all significantly associated with severe cases.⁽¹⁹⁾ In infants presenting with LRT symptoms, the history and physical examination findings can help estimate disease severity.^(1,10) In this study, the severity of RSV was unaffected by the underlying disease but differed from the study by Aikphaibul P et al, which found that children with co-morbidities have a higher risk of severe RSV-associated LRTI.⁽⁵⁾ This difference may be attributable to during the Suphan Buri epidemic, the majority of the children had no underlying disease. A study by Sigurs N found that after the RSV bronchiolitis in infancy, at 7-year follow-up, the RSV influenced the mechanisms involved in the development of asthma by 30% and any wheezing was 68%.⁽²⁰⁾ In this study, when followed children for up to one year after the RSV infection, children with RSV pneumonia and bronchiolitis experienced significant wheezing. RSV may be a significant risk factor for any wheezing, with this effect being most noticeable

in the months following a severe LRTI.

This study had a number of limitations because of its retrospective design; the data of some children about episodes of recurrent wheezing after leaving the hospital was obtained by asking their parents, who could not review medical records because they went to another hospital. Although most viral infections induce a transient airway hyperresponsiveness.^(18,21) If you want to determine whether RSV causes asthma symptoms, longer follow-up studies, greater sample size, blood tests for serum immunoglobulin G antibodies, and lung function tests should be performed to diagnose asthma, which will lead to additional appropriate treatment.

Conclusion

The LRTI caused by RSV is a leading cause of hospitalization in children. In this study, children below 6 months old and those who had clinical lung signs of wheezing were associated with the severity of LRTI from RSV. This information might help physicians caring for these children to provide better support ventilation and early referral to a tertiary hospital for appropriate treatment and prevention of unfavorable outcomes.

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