Factors Associated with Severe Lower Respiratory Tract Infection from Respiratory Syncytial Virus (RSV) in Thai Children

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ABSTRACT

Objective: To determine the factors associated with severe ALRTI from RSV in children.

Materials and Methods: A retrospective study of children aged 1-60 months were conducted from 2014 to 2018. Out of 269 patients diagnosed with RSV ALRTI, 100 children were enrolled in the study, 20 had severe RSV ALRTI, while 80 had non-severe RSV ALRTI as identified by the ReSVinet scale. A multivariable logistic model was conducted to select significant variables.

Results: During the study period, 269 patients were diagnosed with RSV ALRTI. Mean age was 10.45 ± 3.53 months. Clinical manifestations of severe RSV ALRTI group had significant difference in abnormal general condition ($P < 0.001$), tachypnea ($P < 0.001$), $SpO_2 < 85\%$ ($P < 0.001$), poor air entry in lungs ($P < 0.001$), and retraction ($P < 0.001$). The factors associated with severe RSV ALRTI group, were underlying congenital heart disease [aOR 32.45; 95% CI 3.38-311.87, $P = 0.003$] and duration of hospital stay >5 days [aOR 19.56; 95% CI 1.81-212.05, $P = 0.014$].

Conclusion: Factors associated with severe RSV ALRTI in children were underlying congenital heart disease and duration of hospital stay >5 days.

Keywords: Lower respiratory tract infections; respiratory syncytial virus; risk factor (Siriraj Med J 2021; 73: 808-814)

INTRODUCTION

RSV Acute lower respiratory tract infection (ALRTI) causes severe lower respiratory tract illness in the acute phase, leading to hospitalization, higher hospitalization costs, and high mortality rates, especially in young children.[1-4] Approximately 66,000-199,000 died with RSV and 99% of these deaths occurred in developing countries.[5] A study in Thailand reported an annual incidence rate of RSV ALRTI was 5.8-534 cases per 100,000 populations; however, the incidence rate may vary depending on the age demographic and the area where the study is conducted.[6-10]

Thailand is one of the developing countries facing RSV ALRTI problems and there were limited data about severe RSV ALRTI. The data available on RSV infection are insufficient to cause change in the country's policy.[6-10] Thailand has no specific medical treatment and currently using supportive care as the mainstay of management for children with RSV ALRTI, identical to other developing countries.[11] Prophylactic passive immunotherapy using palivizumab - a monoclonal antibody against RSV infection is a costly treatment in Thailand. Presently, palivizumab is not routinely used in Thai children and in other countries. There are many socio-cultural, demographic and environmental risk factors that predispose children to acquire respiratory tract infections especially RSV ALRTI.[12]

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Since there are no updated data for severe RSV ALRTI in Thailand or information about the factors related to severe infection, this study aimed to identify the factors associated with severe RSV ALRTI in children. The benefits of this study include documentation and data confirmation in order to recommend policy changes in Thailand about vaccine prioritization plan or palivizumab dispensation for prophylaxis of the RSV ALRTI.

MATERIALS AND METHODS

Study design and setting

A retrospective case-control study was performed on children were admitted to the the Naresuan University Hospital from 2014 - 2018. The Ethics Committee approved study protocol of the Human Research Study of Naresuan University (No.0897/2019).

Definition

Weight and height of preterm in this study refer to the weight and height of patients' corrected age.

Corrected age is used to adjust the age of preterm participants calculated using the equation: [corrected age = Chronological age + (40 - Gestational age)]

Hospital-acquired pneumonia (HAP) refers to a pneumonia with clinical evidence of a new lung infiltrate caused by an infectious agent (new onset of fever, purulent sputum, leukocytosis, and a decrease in oxygenation) that occurs 48 hours or more after hospital admission and is not incubating at the time of admission. Cultures obtained from endotracheal aspirates are used to identify etiologic agents.

Eligibility criteria

This study enrolled children aged between 1-60 months with acute lower respiratory tract infection (ALRTI) diagnosis from Respiratory Syncytial Virus (RSV) at time of data collection period.

Selection of cases and controls

The data collectors identified children diagnosed with RSV ALRTI then used the ReSVinet scale as the clinical scoring method to assess the disease severity.[13] The subjects were divided into two groups: the severe RSV ALRTI group (cases) and non-severe RSV ALRTI group (controls). The evaluation process utilized 7 parameters (feeding intolerance, medical intervention, respiratory difficulty, respiratory frequency, apnea, general condition, fever) that were assigned different values (from 0 to 3) for a total of 20 points. A score greater than or equal to 14 is classified as severe RSV ALRTI. The control group was selected based on ReSVinet scale score below 14 points, and applied gender matching.

Laboratory method

Nasopharyngeal swab specimens are processed using the Quick Navi™-RSV2 immunoassay (immunochromatographic assay technique) (Denka Seiken Co., Ltd., Tokyo, Japan) to identify RSV.

Sample size determination

Population was estimated from the study of Zhang XB and et al.[14] using a case-control study with binary formula outcomes. Low birthweight, congenital heart disease, bronchopulmonary dysplasia, and airway abnormalities were found to be risk factors for severe respiratory syncytial virus-associated acute lower respiratory tract infections ($p < 0.001$).

P(exposure|case) = The proportions of exposure to severe respiratory syncytial virus-associated acute lower respiratory tract infections was 0.315.

P(exposure|control) = The proportions of exposure to non- severe respiratory syncytial virus-associated acute lower respiratory tract infections was 0.685.

Twenty patients from case group (severe RSV ALRTI) and 80 patients from control group (non-severe RSV ALRTI) were results of the calculations using P(exposure|case) = 0.315, P(exposure|control) = 0.685, Ratio (case:control) = 1:4, Alpha = 0.05, Beta = 0.20.

Sampling procedure

The subjects were patients diagnosed with RSV ALRTI. Those who scored greater than or equal to 14 in the ReSVinet scale were assigned to the severe RSV ALRTI group (case group), while subjects with scores below 14 points were in the non-severe RSV ALRTI (control group). Matlab-program[15] was used to generate a 1:4 (case: control) ratio, matching the sex and age of the participants at random to complete the data.

Collected data

Naresuan University Hospital is a tertiary-care University hospital in the lower northern part of Thailand, all admissions were recorded in the hospital's database. Coders enter the of clinical diagnoses information using the International Classification of Disease 10th revision (ICD-10). We identified subjects with a principal diagnosis of acute bronchitis, bronchiolitis, pneumonia, laryngotracheobronchitis and epiglottitis using the 'J20, J21, J12, J05' ICD-10 codes (J205- acute bronchitis due to respiratory syncytial virus, J209 - acute bronchitis, unspecified, J210-acute bronchiolitis due to respiratory syncytial virus, J219-acute bronchiolitis, unspecified; J121- Respiratory syncytial virus pneumonia, J129 -viral pneumonia, unspecified; J050-Acute obstructive laryngitis[croup], J051-Acute epiglottitis). We confirmed

the RSV diagnosis through laboratory reports. Data gathered were reviewed from the medical records.

Collected data comprised of the date of admission, age, gender, weight, height, preterm birth, underlying diseases, length of hospital stay, daycare attendance, history of exposure to sick patients, second-hand smoke, duration of illness prior to admission. Two physicians (1 medical doctor, 1 pulmonologist) determined the ReSVinet scale scores based on the patients admission records and scores were used to categorize the case and control groups. The data of illness were collected such as general condition, fever, respiratory frequency, lung sound, chest wall retraction, SpO_2, history of apnea, decreased appetite, and complications (e.g. secondary bacterial infection), the clinical course (e.g. requiring intensive care, mechanical ventilation, requiring oxygen supplement).

Data and statistical analysis

The patients were divided into two groups, severe RSV ALRTI and non-severe RSV ALRTI, based on the score of the ReSVinet scale. Continuous variables were compared between the two groups using the Student's t-test. Categorical variables were compared using the Chi square test or Fisher's exact test. Multiple logistic regression analysis was used to identify the independent factors associated with severe RSV ALRTI. All potential risk factors showing a p value of <0.2 in the univariate analysis were included in the regression model. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. Multiple logistic regression analysis was performed to evaluate adjusted odds ratio (AOR) and 95% confidence interval (95% CI). A two-tailed p-value of <0.05 was considered statistically significant. The statistical analysis was performed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Two hundred sixty-nine children between 1-60 months old were diagnosed with RSV ALRTI and were admitted in Naresuan University hospital during the course of the study. The participants were divided into two groups using the ReSVinet scale method: twenty in the severe RSV ALRTI group and 249 in the non-severe RSV ALRTI group. The 249 patients in non-severe RSV ALRTI were further divided using Matlab-program to generate 80 participants randomly matched by sex and age, and to satisfy the 1:4 (case:control) ratio (Fig 1). The record showed RSV ALRTI from March to November, but the upsurge of cases was between August to November and documented the highest number in September. Mean age was 10.45 ± 3.53 months. The mean weight in severe

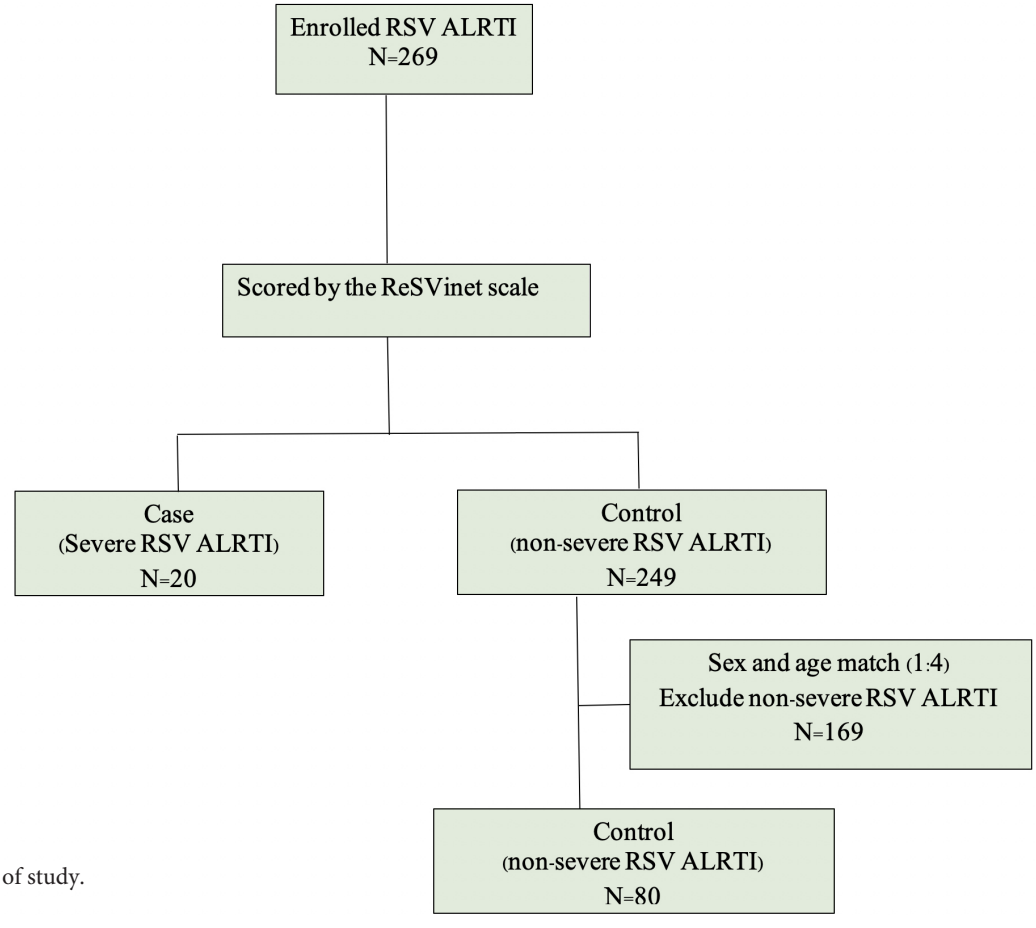

Fig 1. Method of study.

RSV ALRTI group was considerably lower than non-severe RSV ALRTI group (7.20±1.18 kg vs. 9.71±0.45 kg, $P = 0.022$). The mean height in the severe RSV ALRTI group was 67.25±16.12 cm. and non-severe RSV ALRTI group was 76.03±13.64 cm. ($P = 0.015$). Non-severe RSV ALRTI cases group had a higher attendance rate at the daycare center than severe RSV ALRTI group (32.5% vs 5.0%, $P = 0.013$). The age, history of exposure to sick patients, preterm birth, and second-hand smoke contact had no significant difference in both groups. There was a statistically significant difference in the proportion of patients with underlying disease between two groups, 70.0% in severe RSV ALRTI group while only 21.2% non-severe RSV ALRT group ($P < 0.001$). Congenital heart disease and pulmonary disease were the most prevalent underlying conditions in severe RSV ALRTI group (30.0% and 20.0%, respectively). The occurrence bronchopulmonary dysplasia (BPD) in severe RSV ALRTI group was higher than the non-severe RSV ALRTI group but not significantly different (10.0% vs 1.3%, $P = 0.287$). There was a substantial difference in the duration of illness before hospitalization ≤3 day-period and the duration of hospital stay in >5 day-period. The respective results were 65.0% vs. 38.7% ($P = 0.034$) and 95.0% vs. 62.5% ($P = 0.005$) in severe RSV ALRTI group and non-severe RSV ALRTI group. (Table 1).

TABLE 1. Characteristics data and factors associated of participants with severe RSV ALRTI and non-severe RSV ALRTI.

Demographic data	Severe RSV ALRTI (n=20)	Non-severe RSV ALRTI (n=80)	*P* value
Age (months) (mean, SD)	10.45 (3.53)	14.94 (1.32)	0.160[c]
Sex number (%)			0.158[a]
Male	6 (30.0%)	24 (30.0%)	
Female	14 (70.0%)	56 (70.0%)	
Weight (kg) (mean, SD)	7.20±1.18	9.71±0.45	0.022[c]*
Height (cm.) (mean, SD)	67±16.12	76.03±13.64	0.015[c]*
Daycare attendance	1 (5.0%)	26 (32.5%)	0.013[a]*
History of exposure to sick patients	4 (20.0%)	28 (35.0%)	0.198[a]
Preterm birth	6 (30.0%)	9 (11.2%)	0.072[b]
Exposure to second-hand smoke	0 (0.0%)	0 (0.0%)	N/A
Underlying disease	14 (70.0%)	17 (21.2%)	<0.001[a]*
Congenital heart disease	6 (30.0%)	3 (3.8%)	0.002[b]*
Pulmonary disease	4 (20.0%)	9 (11.3%)	0.287[b]
Asthma and allergic rhinitis	2 (10.0%)	8 (10.0%)	
BPD	2 (10.0%)	1 (1.3%)	
Hematologic disease	1 (5.0%)	2 (2.5%)	0.492[b]
Neurologic disease	2 (10.0%)	2 (2.5%)	0.178[b]
Other underlying disease	1 (5.0%)	1 (1.3%)	0.362[b]
Duration of illness prior to admission			
≤3 days	13 (65.0%)	31 (38.7%)	0.034[a]*
>3 days	7 (35.0%)	49 (61.3%)	
Duration of hospital stay >5 days	19 (95.0%)	50 (62.5%)	0.005[a]*
Complications			
HAP	19 (95.0)	38 (47.5)	< 0.001[a]*
Requiring ICU	18 (90.0)	3 (3.8)	< 0.001[a]*
Oxygen supplementation			< 0.001[b]*
Low flow	1 (5.0)	74 (92.5)	
High flow and non-invasive	5 (25.0)	6 (7.5)	
Mechanical ventilator	14 (70.0)	0 (0.0)	

[a]Chi-Square Tests, [b]Fisher's Exact Test, [c]Independent t-test, *p<0.05,

Abbreviations: N/A = Not available, BPD = Bronchopulmonary dysplasia, HAP= Hospital-acquired pneumonia, ICU= intensive care unit

On first-time admission, clinical manifestations of patients with severe and non-severe RSV ALRTI had significant differences in tachypnea (for infant <2 months, respiratory rate >60 /min; for children 2-12 months, respiratory rate >50 /min; for children >1-5 years, respiratory rate >40 /min) ($P < 0.001$), SpO_2 <85% ($P < 0.001$), lung sound (poor air entry) ($P < 0.001$), and all retraction (suprasternal notch, intercostal and subcostal retraction) ($P < 0.001$). In contrast, there were no statistical differences in relation to abnormal general condition (e.g. lethargy, discomfort, agitation), fever and decreased appetite in both groups. No apnea was observed in all patients.

When compared to patients with non-severe RSV ALRTI, patients with severe RSV ALRTI had a higher rate of HAP (95.0% vs. 47.5%, $P < 0.001$). The common pathogens of HAP found in our study were aerobic gram-negative bacilli [*Acinetobacter baumannii* (95%), *Pseudomonas aeruginosa* (2%), *Escherichia coli* (1.8%), *Klebsiella pneumoniae* (1%), Enterobacter spp. (0.2%)].

In addition, the number of patients with severe RSV ALRTI that required intensive care and mechanical ventilation was higher than the number of cases of non-severe RSV ALRTI (90.0% vs 3.8%, $P < 0.001$ and (70.0% vs.0.0%, $P < 0.001$, respectively). All patients needed oxygen supplementation during admission.

Our research recorded four patient deaths (4.0%), three of them had underlying congenital heart diseases [1 case with dextrocardia, ventricular inversion, pulmonary stenosis (PS), patent ductus arteriosus (PDA); 1 case with CoA; and 1 case with ventricular septal defect (VSD)], and one had underlying asthma, all of whom were in the severe RSV ALRTI group.

The results of the multiple logistic regression analysis adjusted by sex, age, daycare center attendance, and duration of illness prior to admission 3 days revealed the following risk factors for severe RSV ALRTI: underlying cardiovascular disease [aOR 32.45; 95% CI 3.38-311.87, $P = 0.003$], and hospital stay >5 days [aOR 19.56; 95% CI 1.81-212.05, $P = 0.014$] (Table 2).

DISCUSSION

This study showed that underlying cardiovascular diseases particularly congenital heart disease is one of the risk factors for severe RSV ALRTI (aOR = 32.45), which is comparable to previous studies.[14,16-21] Infants with congenital heart disease have increased risk for severe RSV ALRTI with higher morbidity (need for assisted ventilation and longer duration of oxygen supplementation) and higher mortality rate of 37% as first reported by MacDonald, et al.[22] Congenital heart disease and RSV-related rehospitalization rate were recorded at 3.0-16.4% in developed countries.[16-19,21,23,24] This study supports the hypothesis that congenital heart disease (CHD) increases the risk for severe RSV ALRTI.

Furthermore, the present study revealed that a hospital stay of more than 5 days is also a concomitant risk factor for severe RSV ALRTI, which is approximately 20 times more common than non-severe RSV ALRTI. This finding may suggest that care providers pay more attention to this group due to the slow recovery from disease and the need to avoid HAP. In our study, HAP was found to be 95.0% in the severe RSV ALRTI group. As a result, patients may undergo procedures to avoid disease-related complications, such as the insertion of intravenous catchers for fluid resuscitation and dehydration, intravenous antibiotics in case of bacterial superinfection, or airway suctioning for clearing secretions. Appropriate management which consists of alcohol-based disinfection and hand washing with alcohol-based rubs or soaps, is extremely effective in reducing RSV transmission and preventing nosocomial infections. We found that nosocomial infection was associated with severe RSV ALRTI group ($P < 0.001$) and the most common pathogen was *Acinetobacter baumannii*

TABLE 2. Multivariable analysis of risk factors of severe RSV-associated acute lower respiratory tract infections.

Factors	Multivariable analysis		
	AOR	95% CI	*P* value
Underlying cardiovascular disease	32.45	3.38-311.87	0.003
Duration of hospital stay >5 days	19.56	1.81-212.05	0.014

Adjusted by sex, age, daycare center attendance, duration of illness prior to admission ≤ 3 days

as reported by other studies.[20,22,25,26] The number of infants admitted to hospitals during RSV season can be very high, resulting in overcrowded pediatric wards and an excessive workload for the staff. Furthermore, staying in the hospital for longer periods of time may increase the risk of cross-bacterial antimicrobial resistance infections. Thus, the importance of systematic preventive measures such as isolation of infected infants in single rooms, and handwashing are highly recommended.

Groothuis, et al[27] were the first to study the burden of early rehospitalization in infants with BPD due to RSV infection. However, we do not consider preterm birth and BPD as associated factors for severe RSV ALTI (*P* 0.287). This is so because our study had recorded preterm births of 6 out of 20 patients with severe RSV ALRTI (30.0%) and 9 out of 80 from non-severe RSV ALRTI group (11.2%) (*P* = 0.072). Moreover, the number of patients with underlying BPD was small (2 out of 20 (10.0%) patients from severe RSV ALRTI group and 1 out of 80 (1.3%) from non-severe RSV ALRTI group), and the majority of the patients in both groups were born at term (70% in severe RSV ALRTI and 89.8% in non-severe RSV ALRTI).

Multivariable analysis revealed that daycare attendance, direct contact with sick patients prior to hospital admission, duration of illness prior to admission, and history of exposure to sick patients were not considered as risk factors for severe RSV ALTI, which contradicted the results of previous studies conducted in developed countries.[16,23,28] This is partly explained by the limited utilization of daycare centers in the study population particularly in patients with severe RSV ALRTI (5%).

A number of limitations should be considered in this current study. First, this research is retrospective, wherein the ReSVinet scores of the participants were based on their admission records instead on the peak of severity of the disease. Second, this cross-sectional study has small sample size. Finally, a full range PCR for the respiratory viral panel could not be performed. Notwithstanding these limitations, prospective studies should be carried out to clarify the correlation of associated factors.

CONCLUSION

Our study demonstrated that factors associated with severe RSV ALRTI in children include underlying cardiovascular diseases and duration of hospital stay > 5 days.

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Conflicts of interest: ALL of the authors declare no conflict of interest.

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