FACTORS ASSOCIATED WITH SEVERE COMMUNITY-ACQUIRED PNEUMONIA IN THAI CHILDREN

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Abstract. Community-acquired pneumonia (CAP) is an important cause of morbidity and mortality in children aged <5 years. There are many factors associated with the severity of pneumonia. We aim to identify factors associated with severe pneumonia in order to apply in clinical practice to guide treatment decisions and health promotion. Study subjects were chosen consecutively from both pediatric intensive care unit and pediatric ward of Chiang Mai University Hospital. Inclusion criteria for study subjects were: 1 month-15 years old children who were diagnosed of having CAP. Exclusion criteria for study subjects were children who were diagnosed of hospital-acquired pneumonia (HAP) or ventilator associated pneumonia (VAP). Parents and children with communication barriers and parents or children who refused to give their consents were excluded. Study subjects were classified by level of pneumonia severity using the PRESS scoring system for children. This study was conducted prospectively from April 2018 to September 2019. We recorded demographic and laboratory data, other important selected information, such as exposure to second-hand cigaretter smoke, and the PRESS scores. We used binary logistic regression analysis to evaluate factors potentially associated with severe pneumonia in the study subjects. During the study period, there were 5,756 pediatric admissions; of these 322 children (5.6%) was diagnosed of having CAP and were included in the study. Fifty-six point eight percent of the study subjects were males and the median age (range) was 26 (1-171) months. In our study, 64.0% of subjects had severe pneumonia, defined as a PRESS score of 4-5, and 36.0% had non-severe pneumonia, defined as a PRESS score of <4. Factors significantly associated with severe pneumonia among study subjects were: exclusive breastfeeding for <6 months (odds ratio (OR) = 2.10; 95% confidence interval (CI): 1.15-3.85; p=0.016); history of exposure to passive smoke (OR = 3.35; 95%CI: 1.98-5.68; p<0.001) and lobar infiltration on chest x-ray (OR = 2.30; 95% CI: 1.37-3.86; p=0.002). These factors need to be taken into consideration when developing methods to prevent severe community acquired pneumonia in this study population. Further studies are needed to determine if these interventions can reduce the incidence of community acquired pneumonia in the study population.

Keywords: associated factors, severe pneumonia, community-acquired pneumonia, children

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INTRODUCTION

Community acquired pneumonia (CAP) is a major cause of morbidity in children. Globally, pneumonia is the main cause of pediatric death in 2016, approximately 16% of 5.6 million deaths of children aged <5 years (UNICEF/WHO, 2006; UNICEF, 2017). The annual childhood pneumonia incidence was 34-40 cases per 1,000 children per year in the United States and Europe (Ostapchuk *et al*, 2004; Jokinen *et al*, 1993). In developing country, more than 150 millions episodes of pneumonia occurrence every year among children under 5 years, accounting for >95% of all new cases (UNICEF/WHO, 2006) and the incidence of pneumonia is estimated around 0.29 episodes per child per year (UNICEF/WHO, 2006). Children with pneumonia between 11 million and 20 million require hospitalization while over 2 million cases pass away from the disease (UNICEF/WHO, 2006). In addition to morbidity and mortality, CAP has other costs, such as increased expenses, hospitalization costs and loss of income (Sabin *et al*, 2020; Zhang *et al*, 2016).

There are various types of organisms resulting in pneumonia in children. The most common cause of pneumonia in preschool-aged children is virus while *Streptococcus pneumoniae* is the most common bacterial pathogen in childhood pneumonia. Moreover, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* usually are the pathogens in children >5 years and adolescents (Ostapchuk *et al*, 2004). Consequently, the child's age is substantial for pneumonia etiology and diagnosis.

Recent studies revealed several factors associated pneumonia in children. Rudan *et al* (2008) reviewed the risk factors leading to childhood pneumonia incidence including lack of exclusive breastfeeding, malnutrition, indoor air pollution, low birth weight, crowding and lack of measles immunization. A previous study found that low literacy status of the mother, inappropriate immunization for age, cooking fuel other than liquid petroleum gas, low socioeconomic status, overcrowding and upper respiratory tract infection in family were significant cause of severe pneumonia in children <5 years (Gupta and Bhadrala, 2019). Another study showed that comorbidity, delay in seeking treatment for 3 days or more and contact with upper respiratory tract infection were independent risk factors for severe pneumonia in children aged 2-59 months while receiving antibiotics at home was a protective factor (Onyango *et al*, 2012).

Previous study from Thailand, Kanlayanaphotporn *et al* (2004) reported the peak incidence of pneumonia was at 1,418 per 100,000 children under 5 years. Another study by Teeratakulpisarn *et al* (2012) reported 73% of all pediatric out patient department (OPD) visits with acute lower respiratory tract infection (ALRI) were children under 5 years (Teeratakulpisarn *et al*, 2012). One-fourth of them required hospitalization and 13.2% of ALRI chidren were diagnosed pneumonia leading cause of both admissions and mortality accounted for 3.22% and 11.29/100,000 population for this age group, respectively

The assessment of severity of CAP is often based on the practitioner's experience. However, there are several pneumonia severity assessment tools for children. The Department of Pediatrics, National Hospital of Yokohama, developed the Pediatric Respiratory Severity Score (PRESS) in order to assess

the severity of respiratory tract infections in children and evaluate the subject in the prehospital setting (Miyaji *et al*, 2015). In this study we used the PRESS in order to categorize our study subjects into severe or non-severe CAP cases. Knowing the factors associated with severe pneumonia will lead to proper treatment decsions and health promotion.

MATERIALS AND METHODS

Study design

This study was a single-center, prospective observational study at a tertiary care hospital, Chiang Mai University Hospital. The study was conducted during April 2018 to September 2019.

Study subjects

Inclusion criteria for study subjects were 1 month-15 years old children who were diagnosed CAP. Exclusion criteria for study subjects were children who were diagnosed hospital-acquired pneumonia (HAP) or ventilator associated pneumonia (VAP). Parents and children with communication barriers and parents or children who refused to give their consents were excluded.

Community acquired pneumonia case detection

In this study only subjects with community acquired pneumonia (CAP) were included. The diagnostic criteria used to define CAP in our study were: 1) acute lower respiratory tract infection (ALRI) acquired in a previously healthy person; 2) the symptoms including fever, cough, dyspnea, tachypnea with supporting evidence of parenchymal infection and inflammation which was diagnosed by chest auscultation or the presence of opacity on the chest radiograph (Gereige and Laufer, 2013; Messinger *et al*, 2017). Tachypnea was defined by a respiratory rate (RR) ≥60 breaths/minute for subjects aged <2 months; ≥50 breaths/minute for subjects aged 2-12 months; ≥40 breaths/minute for subjects aged 1-5 years; ≥30 breaths/minute for subjects aged >5 years (Bradley *et al,* 2011). Dyspnea was defined by the use of accessory muscles during respiration such as nasal flaring and suprasternal, subcostal , intercostal retractions or grunting. Chest auscultation was defined by abnormal adventitious sounds including wheezing, crepitations, rhonchi or bronchial breath sounds.

Classification of pneumonia severity

The Pediatric Respiratory Severity Score (PRESS) is a tool used to classify severity of pneumonia (Miyaji *et al*, 2015). The PRESS score consists of 5 parts with either 0 or 1 point given for each part as follows: respiratory rate at rest on room air (no tachypnea = 0 points, tachypnea, as defined above = 1 point); the presence of wheezing (no wheezing = 0 points, wheezing = 1 point); the use of accessory muscles of respiration (no use of accessory muscles = 0 points, use of accessory muscles = 1 point); oxygen saturation on room air (≥95% = 0 points, <95% = 1 point) and feeding difficulties (no feeding difficulties = 0 points, feeding difficulties = 1 point). A total PRESS score of 4-5 points was defined as severe CAP and <4 points was defined as not severe (Miyaji *et al*, 2015).

Statistical Analysis

Statistical analysis was carried out using IBM Statistical Package for the Social Sciences (SPSS) for Windows, Version 23.0 (IBM Corp, Armonk, NY). Demographic data were classified using descriptive statistics. Normally distributed continuous variables were compared using

the student's t-test and skewed continuous variables were compared using the Mann-Whitney U test. Categorical data were evaluated using the Chi-square test or Fisher's exact test. A p-value <0.05 was considered to be statistically significant. Logistic regression analysis was used to detect factors significanly associated with severe pneumonia.

Ethical consideration

This study was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University Hospital (Approval No. 5294). Informed consent were obtained from the parents of the children enrolled in the study.

RESULTS

A total of 322 subjects were included in the study, 56.8% males. The median (range) age of study subjects was 26 (1-171) months (Table 1). Sixty-six point eight percent of subjects were exclusively breastfed during the first 6 months of life. Thirty-five point four percent of subjects had a history underlying disease, consisting of chronic lung disease (8.1%), congenital heart disease (7.8%), neuromuscular disorder (4.7%), allergic rhinitis (4.0%), thalassemia (3.7%), hematologic malignancy (3.1%), nephrotic syndrome (1.6%), short bowel syndrome (1.6%) and multiple anomalies (0.9%).

Forty-six percent of subjects attended daycare and 52.0% were exposed to second-hand smoke at home. Eighty-seven percent of subjects were up to date on their Extended Program of Immunization (EPI) vaccinations. They were also up to date on non-EPI vaccinations, namely, influenza vaccine, pneumococcal vaccine and haemophilus influenzae type b (Hib) vaccine at 29.8%, 22.7% and 70.5%, respectively.

The most common abnormal finding on chest x-ray was a lobar infiltration (44.1%) followed by a perihilar infiltration (35.4%), an interstitial infiltration (18.9%) and hyperinflation without a specific infiltration (1.6%). The median (range) length of stay in the hospital was 5 (4-7) days.

Thirty-six percent of subjects had a PRESS score classifying them as having non-severe pneumonia and 64.0% had a PRESS scoring classifying them has having severe pneumonia. According to univariate analysis, the factors associated with severe pneumonia included body weight (p=0.029), a history of breastfeeding for <6 months (p<0.001), underlying disease (p=0.015), exposure to second-hand smoke (p<0.001), hemoglobin level (p=0.008), a presence of infiltration on chest X-ray (p<0.001) and length of stay in hospital (p<0.001). However, we found no significant association between severe pneumonia and the following factors: age, sex, history of premature birth, caregiver education level, family income, daycare attendance, vaccination status, white blood cell count, platelet count and serum electrolyte abnormalities (Table 1).

Factors significantly associated with severe pneumonia on logistic regression analysis were: exclusively breastfeeding for <6 months (adjusted odds ratio (adjusted OR)) = 2.10; 95% confidence interval (CI): 1.15-3.85; p=0.016), having a history of being exposed to second hand smoke (OR = 3.35; 95% CI: 1.98-5.68, p<0.001) and having a lobar infiltration on chest x-ray (OR = 2.30; 95% CI%: 1.37-3.86, p=0.002). In our study, we found no association on logistic regression analysis between severe pneumonia and the following: body weight category, history of underlying disease and hemoglobin level classification (Table 2).

Table 1
Selected factors among study subjects by pneumonia severity status.

Factors	Severity of pneumonia		*p-value*
	Non-severe (*n*=116)	Severe (*n*=206)	
Age in months	25.0 (11.0-46.5)[a]	26.5 (15.8-41.0)[a]	0.494
Aged ≤2 years, *n* (%)	59 (50.9)	94 (45.6)	0.367
Male, *n* (%)	69 (59.5)	114 (55.3)	0.471
Body weight in kg	9.6 (5.0-12.0)[a]	11.3 (7.8-14.0)[a]	0.029[b]
History of preterm birth (<37 weeks GA), *n* (%)	15 (12.9)	44 (21.4)	0.061
Exclusively breastfed for < 6 months, *n* (%)	21 (18.1)	86 (41.7)	<0.001[b]
No underlying disease, *n* (%)	85 (73.3)	123 (59.7)	
Underlying disease			0.015[b]
Chronic lung disease, *n* (%)	5 (4.3)	21 (10.2)	
Congenital heart disease, *n* (%)	3 (2.6)	22 (10.7)	
Neuromuscular disease, *n* (%)	6 (5.2)	9 (4.4)	
Caregiver education level			0.055
Primary school	16 (13.8)	51 (24.8)	
Secondary school	42 (36.2)	71 (34.5)	
Higher education	58 (50.0)	84 (40.8)	
Income			0.581
<500,000 THB/year	99 (85.3)	183 (88.8)	
500,001-1,000,000 THB/year	15 (12.9)	18 (8.7)	
>1,000,001 THB/year	2 (1.7)	5 (2.4)	
Daycare attendance, *n* (%)	48 (41.4)	100 (48.5)	0.216
Exposure to second-hand smoke, *n* (%)	35 (30.2)	133 (64.6)	<0.001[b]
Incomplete EPI vaccination for age, *n* (%)	15 (12.9)	27 (13.1)	0.964
Influenza vaccine, *n* (%)	28 (24.1)	68 (33.0)	0.095
Pneumococcal vaccine, *n* (%)	25 (21.6)	48 (23.3)	0.719
Hib vaccine, *n* (%)	75 (64.6)	152 (73.8)	0.085
Hemoglobin in g/dl	11.6 (10.6-12.5)[a]	12.0 (10.9-13.0)[a]	0.008[b]
White blood cell count in cells/mm^3 of blood	11,975.0 (9,592.0-18,145.0)[a]	12,195.0 (8,715.0-16,010.0)[a]	0.314
Platelet count in cells/mm^3 of blood	375,500.0 (291,000.0-471,250.0)[a]	358,000.0 (276,500.0-434,000.0)[a]	0.196

Table 1 (Continued)

Factors	Severity of pneumonia		*p-value*
	Non-severe (*n*=116)	Severe (*n*=206)	
Sodium in mmol/l of blood	138.0 (136.0-140.0)[a]	138.0 (136.0-140.0)[a]	0.323
Potassium in mmol/l of blood	3.9 (3.5-4.2)[a]	3.8 (3.5-4.2)[a]	0.161
Chloride in mmol/l of blood	101.0 (99.0-104.0)[a]	101.0 (98.0-104.0)[a]	0.536
Total CO_2 in mmol/l of blood	18.0 (17.0-20.0)[a]	18.0 (16.0-20.0)[a]	0.497
Chest X-ray			<0.001[b]
Lobar infiltration, *n* (%)	35 (30.2)	107 (51.9)	
Perihilar infiltration, *n* (%)	46 (39.6)	68 (33.0)	
Interstitial infiltration, *n* (%)	32 (27.6)	29 (14.1)	
Hyperinflation without specific infiltration, *n* (%)	3 (2.6)	2 (0.9)	
LOS in hospital in days	5.0 (3.0-7.0)[a]	7.0 (5.0-10.0)[a]	<0.001[b]

[a]median (interquartile range); [b]statistically significant at $p < 0.05$; CO_2: carbon dioxide; dl: decilitre, EPI: Expanded Programme on Immunization; g: gram; GA: gestational age; Hib: *Hemophillus influenza* type b; kg: kilogram; LOS: length of stay; mm^3: cubic millimeter; mmol/l: millimoles per liter; THB: Thai Baht.

DISCUSSION

In our study, children who breastfed for <6 months had a greater chance of having severe pneumonia. Breastfeeding has been previously reported to decrease the risk for pneumonia (Victora *et al*, 1999). César *et al* (1999) found infants who were not breastfed had a 17 times greater risk of being hospitalized with pneumonia. Broor *et al* (2001) studied children aged <5 years and found lack of breastfeeding was associated with severe pneumonia as well as maternal upper respiratory, having a sibling with an upper respiratory infection, having severe malnutrition, having someone in the house use cooking fuel other than liquid petroleum gas, not being up to date on immunizations for age and having a history of a lower respiratory tract infection in the family. Lamberti *et al* (2013) found the mortality rate was higher among those not breastfed than those who exlusively breastfed.

In our study, children who were exposed to second-hand cigarette smoke were more likely to have severe pneumonia. Tobacco has been reported to increase the risk for pneumonia (Quinton *et al*, 2018). Ahn *et al* (2015) reported CAP hospitalized children who had two or

Table 2
Factors associated with severe pneumonia.

Factors	Severity of pneumonia		Adjusted odds ratio (95% CI)	*p*-value
	Non-severe (*n*=116)	Severe (*n*=206)		
Body weight in kg	9.6 (5.0-12.0)[a]	11.3 7.8-14.0)[a]	-	0.471
Exclusively breastfed for <6 months, *n* (%)	21 (18.1)	86 (41.7)	2.10 (1.15-3.85)	0.016[b]
History of underlying disease, *n* (%)	31 (26.7)	83 (40.3)	-	0.286
History of exposure to second-hand smoke, *n* (%)	35 (30.2)	133 (64.6)	3.35 (1.98-5.68)	<0.001[b]
Hemoglobin in g/dl	11.6 (10.6-12.5)[a]	12.0 (10.9-12.9)[a]	-	0.096
Lobar infiltration on chest x-ray, *n* (%)	35 (30.2)	107 (51.9)	2.30 (1.37-3.86)	0.002[b]

[a]median (interquartile range); [b]statistically significant $p< 0.05$; CI: confidence interval; dl: deciliter; g: gram; kg: kilogram.

more smokers in the house significantly more likely needed a longer length of hospitalization and significantly more likely required intensive care than children whose no one in the house smoked. Several studies have reported living in a house with smokers was significantly associated with having pneumonia of greater severity (Jroundi *et al*, 2014; Karki *et al*, 2014; Hassan *et al*, 2001). Hassan *et al* (2001) found smoking at home and weaning from breast milk before age 6 months were significantly associated with having severe pneumonia.

In our study, subjects with a lobar infiltration in chest x-ray were more likely to have severe pneumonia. A lobar infiltration is often found in but no exclusive to infection due to *Streptococcus pneumoniae* and *Klebsiella pneumoniae* (Nambu *et al*, 2014; Franquet, 2001). Virkki *et al* (2002) reported 71.0% of children with an alveolar infiltrate on the chest x-ray had bacterial pneumonia. Bacterial infection is sometimes associated with a more severe infection and since having an alveolar infiltration on x-ray, it suggests more severe pneumonia was associated with a bacterial infection in our study. Korppi *et al* (1993) reported 74.0% of subjects with an alveolar infiltration had bacterial pneumonia and the remainder had viral pneumonia. However, Turner *et al* (1987) reported that alveolar infiltration were found in 5 of 13 (38%) patients with bacterial pneumonia compared with 16 of 24 (67%) patients diagnosed viral infection. Children with an alveolar infiltration on radiograph should be monitored more closely for signs and symptoms of worsening infection.

A limitation of our study was that it was conducted at a single tertiary care hospital among admitted patients only. These results cannot be applied to other populations. Another limitation

in our study was that some factors were not asked about in history, such as recently receiving antibiotics at home, having siblings with an upper respiratory tract infection, having a subject with severe malnutrition, having a history of a delayed diagnosis or treatment, having a history of a respiratory tract infection in other members of the family and the types of organisms causing the infection. Another limitation was the used of the PRESS score to classify the severity of pneumonia making it impossible to compare to other studies using other systems to classify pneumonia severity. Further studies are needed in multiple centers among both in- and out-patients so the results can be applied to other populations.

Severe pneumonia is relatively common in our study population and the factors significantly associated with it were exposure to second-hand cigarette smoke, discontinuing breastfeeding prior to age 6 months and having a lobar infiltration on a chest x-ray. Children with these factors should be monitored closely when diagnosed with pneumonia. Mothers should be encouraged to exclusively breastfeed their children for at least 6 months and parents should make an effort to prevent their children from being exposed to second-hand cigarette smoke.

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CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflict of interest.

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