Original Article

Differentiating Viral and Bacterial Pneumonia by Clinical Manifestations among Children in Chiang Mai, Thailand

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Background: Viral pneumonia is a common complication of influenza like illness including COVID-19. Virus is the most common cause of pneumonia in children. While there are important cues in history, the laboratory examination that can help differentiate viral and bacterial causes. There are limited clinical manifestations to differentiate viral and co-infection bacterial and viral pneumonia.

Objective: To determine basic clinical manifestations and laboratory performed at bedside as predictors to differentiate viral and co-infection bacterial and viral pneumonia.

Materials and Methods: A retrospective study was conducted in pediatric patients with radiographic evidence of severe pneumonia and admitted in Nakornping Hospital, Chiang Mai, Thailand between October 2017 and April 2020. Multiplex real time polymerase chain reactions (PCRs) (RP-24-26) were used to identify the cause of the pneumonia. Demographic data and basic clinical predictors such as age, comorbidity, symptoms, and physical findings, and basic laboratory such as complete blood count were collected. Patients were divided into three groups, no infection detected, viral infection, and bacterial and viral co-infection. Polytomous logistic regression was performed to investigate predictors for type of infection. Area under the receiver operating characteristic curve (AuROC) and 95% confidence interval (CI) were further determined for a final model to differentiate type of infection.

Results: Two hundred eight cases participated in this study and included 122 males (58.7%). The etiology of pneumonia identified by RP-24-26, pathogen was detected among 166 cases (79.8%). A virus was detected in 141 cases (67.8%), co-infection was detected in 25 cases (12%), and no infection was detected in 42 cases (20.2%). The statistically significant predictor for viral pneumonia was cough, with an adjusted relative risk ratio (RRR) of 4.42 (1.41 to 13.82). The statistically significant predictors for co-infection were age 13 to 24 months and lymphocytes at 40.0% or greater with adj. RRR 14.28 (1.47 to 138.52), and 4.60 (1.24 to 17.04), respectively. Pneumonia patients with cough were 4.42 times more to have viral cause. Those with lymphocytes of 40.0% or greater were 4.60 times more to be co-infected with both virus and bacteria, especially in the age group 13 to 24 months compared with 1 to 12 months. The age group13 to 24 months, cough, and lymphocytes at 40.0% or greater were 74% (95% CI 0.66 to 0.82) correctly predicted to viral pneumonia.

Conclusion: Coughing is a predominant symptom for childhood pneumonia caused by virus. In addition, pneumonia patients age 13 to 24 months who have lymphocyte of more than 40% should start and continue antibiotics until complete course.

Keywords: Childhood pneumonia, Respiratory panel 24, Respiratory panel 26, Co-infection bacterial pneumonia, Predictor

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Pneumonia is one of a leading cause of morbidity and mortality among children. The most common causes of community acquired pneumonia (CAP) in children are respiratory viruses. A previous study conducted between 2010 and 2012 in America[(1)], found that the majority of CAP was caused by a virus. The present study detected pathogen in 81%, which 66% was caused by virus, 8% was caused by bacteria, and 7% was caused by virus and bacteria. Viral pneumonia is a leading cause of dead especially in comorbid patients. Viruses can be co-pathogen with bacteria, particularly in those with severe pneumonia

requiring admission to intensive care unit (ICU) and in ventilator-associated pneumonia. In Thailand, a study in severe CAP between June 2013 and May 2014[2] found that 52.7% were positive for respiratory viruses. The most common viruses were respiratory syncytial virus (RSV) (45.8%), rhinovirus (HRV) (22.9%), and adenovirus (AdV) (18.7%).

In patients hospitalized with severe pneumonia, the causative pathogens are unknown. In the past, the epidemiology of the pathogen causing CAP among children was poorly defined. Since 2017, Nakornping Hospital has joined with the Ministry of Public Health in the project "Flu Lab Surveillance". Respiratory secretions were sent to determine the cause of pneumonia by multiplex real time polymerase chain reaction (PCR) for respiratory pathogen Respiratory Panel 26 (RP-26). Later, in 2018, Flu-DARRT project (Strengthen Respiratory Disease Outbreak Detection and response in Thailand) was initiated to determine the cause of pneumonia by multiplex real time PCR for respiratory pathogen Respiratory Panel 24 (RP-24). From both projects, patients with severe pneumonia have been detected with various types of respiratory pathogens. These projects in addition to the benefits of surveillance and disease control also helped provide medical information to improve treatments.

From the results of the RP-24 & RP-26 test, more than one type of respiratory virus were found in patients with severe pneumonia. However, rapid test for influenza and RSV virus is useful for doctor to get quick result to identify the cause of the pneumonia. Though, it may be difficult to attribute causality because it is often impossible to distinguish between organisms colonizing or infecting the upper respiratory tract and those causing pneumonia. Currently available host biomarkers lack accuracy to distinguish bacterial or mixed bacterial-viral infections from viral infections[3]. The limitation of multiplex real time PCR test may have long positive results in persistent infection or prolong pathogen shedding[4] and expensive and non-available in every hospital.

Symptoms and signs of pneumonia may be subtle, particularly in infants and young children. The clinical presentation of childhood pneumonia varies depending upon the responsible pathogen, the particular host, and the severity. The presenting signs and symptoms are non-specific, therefore, no single symptom or sign is pathognomonic for pneumonia in children. Although no single finding reliably differentiates pneumonia from other causes of childhood respiratory illnesses, hypoxia and increasing work of breathing are more important than tachypnea and auscultatory findings[5]. In a multicenter population-based study, 95% had cough, 90% had fever, 75% had anorexia, 70% had dyspnea, and 55% had chest wall retractions[1]. Wheezing is a frequent finding in atypical bacterial and viral pneumonia[6]. The positive predictive value of detected wheezing for viral pneumonia was 96.3%. It is an independent predictor of viral pneumonia[7]. A previous study[8] showed that no clinical or radiological characteristic was helpful to separate among viral, pneumococcal, and atypical bacterial etiology of CAP in children.

The proportion of patients with increased white blood cell (WBC) or erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) did not differ between bacterial and viral pneumonias. The chest X-ray (CXR) with alveolar pneumonia, especially those with lobar infiltration, had laboratory evidence of a bacterial infection. Interstitial infiltrates are seen in both viral and bacterial pneumonias[9]. Other study found that combining the CRP of more than 72 mg per L with either the presence of fever of 38°C or higher or the absence of rhinorrhea improved the discrimination of bacterial from presumed viral pneumonia better than CRP alone[10]. Acute-phase reactants, such as ESR, CRP concentration, or serum procalcitonin (PCT) concentration, cannot be used to distinguish between viral and bacterial causes of CAP[11]. However, in some patients with very high serum PCT, CRP, or interleukin-6 (IL-6) values, bacterial pneumonia is probable[11]. PCT, CRP, and IL-6 tests are not routinely used in Thailand. The present study was conducted to evaluate whether clinical symptoms and preliminary complete blood count (CBC) tests could predict the causes of viral and bacterial pneumonia. The results could be useful to provide treatment or better forecasting the severity of the disease due to limited cues for differentiating bacterial from viral pneumonia by clinical manifestation.

Objective

The present study was to determine basic clinical manifestations and laboratory performed at bedside as predictors to differentiate viral and co-infection bacterial and viral pneumonia.

Materials and Methods

The study design was a retrospective cross-sectional analytical study. The study population were children age between 1-month to less than 18-years-

old admitted to Nakornping Hospital with diagnosis of severe pneumonia classified by the World Health Organization (WHO) criteria and using radiological evidence between October 1 2017 and April 30, 2020.

Inclusion and Exclusion criteria

The inclusion criteria included children aged 1-month to18-years-old diagnosed with severe pneumonia and the children who performed either RP-24 or RP-26 The QIAstat Respiratory Panel® assay (QIAstat RP)[12] to identify etiology of pneumonia from nasopharyngeal swab or tracheal suction secretion. The study excluded patients whose data were incomplete.

Predictors

Study variables were collected from disease investigation forms including patients' demographic data such as gender and age, clinical data such as underlying disease, symptoms and signs on admission day including fever, cough, sore throat, sputum, dyspnea, wheezing, headache, myalgia, and diarrhea, and laboratory data such as WBC, neutrophil, hematocrit (Hct) using a cut-off point at 33%[13], and lymphocyte with a cut-off point at 40%[14].

Definitions

RP-26 refers to the examination under the project Analysis of 26 viral and bacterial pathogens by multiplex real time PCR of the Institute of Public Health Sciences Department of Medical Sciences, Ministry of Public Health.

The genetic material of virus and 26 respiratory pathogens are influenza A virus (FluA), influenza B virus (FluB), RSV A, RSV B, influenza A virus subtype H1, influenza A virus subtype H1pdm09, influenza A virus subtype H3, AdV, enterovirus (HEV), parainfluenza virus 1 (PIV1), parainfluenza virus 2 (PIV2), parainfluenza virus 3 (PIV3), coronavirus, parainfluenza virus 4 (PIV4), metapneumovirus (MPV), bocavirus (HBoV), HRV, coronavirus NL63 (CoV NL63), coronavirus OC43 (CoV OC43), *Mycoplasma pneumoniae* (MP), *Chlamydophila pneumoniae*, *Legionella pneumophila* (LP), *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Bordetella pertussis* (BP), and *Bordetella parapertussis* (BPP) (under project Flu lab surveillance, Enhancement of Thailand's Laboratory Capacity to prepare and Respond for Pandemic Influenza and Viral Emerging Diseases).

RP-24 is a multiplex real time PCR for respiratory pathogen 24 type are AdV, FluA, influenza A H1N1, influenza A H3N2, influenza A unsubtype, FluB, PIV1, PIV2, PIV3, PIV4, HRV A/B/C, RSV A, RSV B, HBoV 1/2/3/4, MPV, coronavirus 229E (CoV 229E), CoV NL63, CoV OC43, HEV, MP, *C. pneumoniae*, LP, BP, and BPP (under project DARRT Strengthen Respiratory Disease Outbreak Detection and response in Thailand).

Severe pneumonia refers to the new classification of WHO, elaborated in 2014. It is pneumonia among children and adolescents with any general danger sign that requires referral and injectable therapy[15].

The present study was approved by the Institutional Review Board of the Nakornping Hospital, Ministry of Public Health, Thailand (no.149/63).

Statistical analysis

Univariable comparisons for demographics, clinical, and laboratory variables were examined across three groups of patients, the no infection, viral infection, and co-infection of virus and bacteria, using polytomous logistic regression. Two-stage analyses were performed by 1) selecting variables with p-value less than 0.100 in univariable analysis into 2) multivariable polytomous logistic regression was then used to determine potential predictors that had statistically significant associations with study outcome with no infection as a reference group. In the last stage, p-value less than 0.05 was set as significance level[16]. Relative risk ratio (RRR), both crude and adjusted, were reported. Furthermore, performances of models with predictors to differentiate viral infection from no infection detected were investigated using binary logistic regression analyses and presented with area under the receiver operating characteristic curve (AuROC). Missing values over 10% of predictors were handled by a multiple imputation method (MI) using logistic regression[17]. The authors analyzed data with Stata, version 14.0 (StataCorp LP, College Station, TX, USA), with p-value of less than 0.05 indicating statistical significance.

Results

Of the 208 cases of severe pneumonia, 122 were males (58.7%). The etiology of pneumonia identified by RP-24-26, pathogens were detected among 166 cases (79.8%). A virus was detected in 141cases (67.8%), co-infection detected in 25 cases (12%), and no infection detected in 42 cases (20.2%). All patients required oxygen therapy and 180 cases (87.8%) required mechanical ventilation (Table 1).

Table 1. Predictors to differentiate viral infection and co-infection of virus and bacteria from RP-24-26 (n=208)

	No infection (n=42)	Viral infection (n=141)	Co-infection (n=25)	Crude RRR (95% CI)	
				Viral infection vs. no infection detected	Co-infection vs. no infection detected
Sex					
Male	22 (52.4)	85 (60.3)	15 (60.0)	1.00	1.00
Female	20 (47.6)	56 (39.7)	10 (40.0)	0.72 (0.36 to 1.45)	0.73 (0.27 to 2.00)
Age (months)					
1 to 12	24 (57.1)	84 (59.6)	12 (48.0)	1.00	1.00
13 to 24	1 (2.4)	29 (20.6)	7 (28.0)	8.28 (1.07 to 64.00)	14.00 (1.54 to 127.22)*
25 to 60	9 (21.4)	14 (9.9)	3 (12.0)	0.44 (0.17 to 1.15)	0.67 (0.15 to 2.92)
>60	8 (19.0)	14 (9.9)	3 (12.0)	0.50 (0.19 to 1.33)	0.75 (0.17 to 3.35)
Median (P25, P75; min-max)	10 (3, 60; 1 to 168)	12 (5, 24; 1 to 228)	13 (5, 19; 1 to 84)	0.99 (0.99 to 1.00)	0.99 (0.98 to 1.00)
Signs and symptoms on admission day					
Fever (T ≥38°C)					
• Yes	36 (87.8)	131 (93.6)	24 (96.0)	2.02 (0.64 to 6.41)	3.33 (0.36 to 30.33)
• No	5 (12.2)	9 (6.4)	1 (4.0)	1.00	1.00
Cough (any cough)					
• Yes	30 (76.9)	129 (94.9)	24 (96.0)	5.53 (1.91 to 16.03)*	7.2 (0.85 to 60.86)
• No	9 (23.1)	7 (5.2)	0 (4.0)	1.00	1.00
History of sputum					
• Yes	31 (77.5)	120 (87.0)	23 (95.8)	1.94 (0.79 to 4.72)	6.68 (0.79 to 56.48)
• No	9 (22.5)	18 (13.0)	1 (4.2)	1.00	1.00
Sore throat					
• Yes	5 (17.9)	29 (26.4)	5 (71.4)	1.65 (0.57 to 4.73)	11.5 (1.71 to 77.18)*
• No	23 (82.1)	81 (73.6)	2 (28.6)	1.00	1.00
Dyspnea					
• Yes	40 (97.6)	130 (94.9)	22 (95.6)	0.46 (0.06 to 3.89)	0.55 (0.13 to 9.23)
• No	1 (2.4)	7 (5.1)	1 (4.4)	1.00	1.00
Wheezing					
• Yes	12 (40.0)	44 (39.6)	9 (69.2)	0.98 (0.43 to 2.24)	3.38 (0.84 to 13.49)
• No	18 (60.0)	67 (60.4)	4 (30.8)	1.00	1.00
Rash					
• Yes	4 (14.3)	8 (7.6)	0 (0.0)	0.49 (0.14 to 1.78)	n/a
• No	24 (85.7)	97 (92.4)	3 (100)	1.00	1.00
Headache					
• Yes	6 (22.2)	10 (10.3)	3 (60.0)	0.40 (0.13 to 1.23)	5.25 (0.71 to 39.03)
• No	21 (77.8)	87 (89.7)	2 (40.0)	1.00	1.00
Muscle pain					
• Yes	6 (23.1)	8 (8.2)	0 (0.0)	0.29 (0.09 to 0.95)*	n/a
• No	20 (76.9)	90 (91.8)	3 (100)	1.00	1.00
Diarrhea					
• Yes	13 (39.4)	30 (24.2)	4 (57.1)	0.49 (0.22 to 1.10)	2.05 (0.39 to 10.70)
• No	20 (60.6)	94 (75.8)	3 (42.9)	1.00	1.00
Underlying disease					
• Yes	9 (22.0)	28 (20.0)	4 (16.0)	0.88 (0.38 to 2.07)	0.68 (0.18 to 2.48)
• No	32 (78.0)	112 (80.0)	21 (84.0)	1.00	1.00
Laboratory					
White blood cell (cells/L×1,000)					
• <15	26 (63.4)	93 (66.0)	15 (60.0)	1.00	1.00
• ≥15	15 (36.6)	48 (34.0)	10 (40.0)	0.89 (0.43 to 1.85)	1.16 (0.42 to 3.21)
• Median (P25, P75; min-max)	12.8 (8.6, 18.9; 4 to 35.2)	12.4 (8.7, 17.0; 1.1 to 45.3)	12.5 (9.2, 19.0; 7.3 to 36.3)	0.99 (0.99 to 1.00)	1.00 (0.99 to 1.00)
Neutrophil (%)					
• <50.0	8 (19.5)	35 (24.8)	9 (36.0)	1.00	1.00
• ≥50.0	33 (80.5)	106 (75.2)	16 (64.0)	0.73 (0.31 to 1.74)	0.43 (0.14 to 1.33)
• Median (P25, P75; min-max)	69.1 (52.7, 78.2; 12 to 88.5)	64.4 (50.2, 77.2; 8.9 to 95.6)	61.8 (44.6, 76.0; 22.3 to 87)	0.99 (0.98 to 1.01)	0.99 (0.96 to 1.01)
Lymphocytes (%)					
• <40.0	33 (80.5)	104 (73.8)	15 (60.0)	1.00	1.00
• ≥40.0	8 (19.5)	37 (26.2)	10 (40.0)	1.47 (0.62 to 3.46)	2.75 (0.90 to 8.36)
• Median (P25, P75; min-max)	25.3 (15.7, 36.9; 5.7 to 70)	27.2 (16.8, 41.0; 2 to 81)	31.3 (16.5, 46.0; 8.9 to 68.7)	1.01 (0.99 to 1.03)	1.02 (0.99 to 1.05)
Hematocrit (%)					
• <33.0	24 (58.5)	68 (48.2)	14 (56.0)	0.66 (0.33 to 1.33)	0.90 (0.33 to 2.46)
• ≥33.0	17 (41.5)	73 (51.8)	11 (44.0)	1.00	1.00
• Median (P25, P75; min-max)	32 (27.2, 37.6; 12.9 to 47.7)	33.2 (30.8, 37.0; 23.6 to 53)	32.9 (27.4, 34.5; 18.8 to 39.2)	1.05 (0.99 to 1.12)	0.97 (0.89 to 1.06)
Platelet count (cells/L×1,000)					
• <150	8 (19.5)	10 (7.1)	0 (0.0)	0.31 (0.12 to 0.86)*	n/a
• ≥150	33 (80.5)	131 (92.9)	25 (100)	1.00	1.00
• Median (P25, P75; min-max)	329 (170, 461; 27 to 767)	333 (239, 426; 26 to 874)	346 (263, 402; 158 to 748)	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)

RRR=relative risk ratio; CI=confidence interval; n/a=not available

* p<0.05 is statistical significance

In cases of sole viral pneumonia, the age that was more common was 13 to 24 months (78.4%) with a median age of 1 year, 69 were male (69.7%), 80% were Thai nationality, 68.3% had underlying disease, 79.8% received antiviral drug, 74.6% received antibiotic, and 68.6% had fever.

Univariable comparisons for demographics, clinical, and laboratory variables across three groups of patients for no infection detected, viral infection, and co-infection of viral and bacterial, showed that age 13 to 24 months and sore throat was statistically significant to predict co-infection with crude RRR (95% confidence interval [CI]) of 14.00 (1.54 to 127.22) and 11.5 (1.71 to 77.18), respectively. Cough, muscle pain, and platelet of less than 150,000 were statistically significant to predict viral pneumonia with crude RRR (95% CI) of 5.53 (1.91 to 16.03), 0.29 (0.09 to 0.95), 0.31 (0.12 to 0.86), respectively (Table 1).

With two-stage analysis, the last model using multivariable polytomous regression revealed three variables that were predictors for viral infection or co-infection using the no infection detected group as a reference. For viral infection, cough was statistically significant with adjusted RRR 4.42 (1.41 to 13.82), while co-infection had age 13 to 24 months and lymphocytes of 40.0% or more as statistically significant with adjusted RRR 14.28 (1.47 to 138.52), and 4.60 (1.24 to 17.04), respectively. It could be interpreted that patients with coughing had 4.42 times more chances to have viral infection, which is the same direction with lymphocytes of 40.0% or more had 4.60 times more chance to be co-infected with virus and bacteria, especially in the age group 13 to 24 months compared with 1 to 12 months (Table 2).

Further analyses to differentiate viral infection from no infection detected, using binary logistic regression analysis among models with different clinical manifestations was done. The best model with the highest AuROC was with age group and cough combined with lymphocytes of 40.0% or more, which correctly predicted viral infection in 74% (95% CI 0.66 to 0.82) (Table 3). The authors compared the two models (3 versus 7) and found statistically significant AuROC ($p<0.001$), which is illustrated in Figure 1.

Descriptive analysis showed that the top five respiratory virus identified were HRV 52 cases (25%), influenza 28 cases (13.5%), RSV 27 cases (13.0%), parainfluenza 25 cases (12%), and AdV 23 cases (11.1%), respectively. Additionally, the present study detected bacteria in 12% with 16 cases (7.7%) of H influenza, 11 cases (5.3%) of *S. pneumoniae*, two

Table 2. Predictors to differentiate between viral infection and co-infection of virus and bacteria from RP-24-26 using multinomial logistic regression analysis (n=208)

Predictors	Adjusted RRR (95% CI)	
	Viral infection vs. no infection detected	Co-infection vs. no infection detected
Age (months)		
1 to 12	1.00	1.00
13 to 24	6.17 (0.77 to 49.26)	14.28 (1.47 to 138.52)*
>24	0.44 (0.19 to 1.01)	0.91 (0.25 to 3.30)
Cough		
Yes	4.42 (1.41 to 13.82)*	5.35 (0.59 to 48.75)
No	1.00	1.00
Lymphocytes (%)		
<40.0	1.00	1.00
≥40.0	1.85 (0.66 to 5.18)	4.60 (1.24 to 17.04)*

RRR=relative risk ratio; CI=confidence interval

* $p<0.05$ is statistical significance

Table 3. Model proposed for viral pneumonia (n=183)

Model	Predictors	AuROC (95% CI)
1	Cough	0.60 (0.52 to 0.66)
2	Cough + wheezing	0.60 (0.48 to 0.71)
3	Cough + lymphocytes ≥40.0	0.63 (0.54 to 0.71)
4	Cough + lymphocytes ≥40.0 + wheezing	0.60 (0.48 to 0.72)
5	Age group + cough	0.73 (0.65 to 0.81)
6	Age group + cough + wheezing	0.66 (0.54 to 0.78)
7	Age group + cough + lymphocytes ≥40.0	0.74 (0.66 to 0.82)
8	Age group + cough + lymphocytes ≥40.0 + wheezing	0.68 (0.56 to 0.79)

AuROC=area under the receiver operating characteristic curve; CI=confidence interval

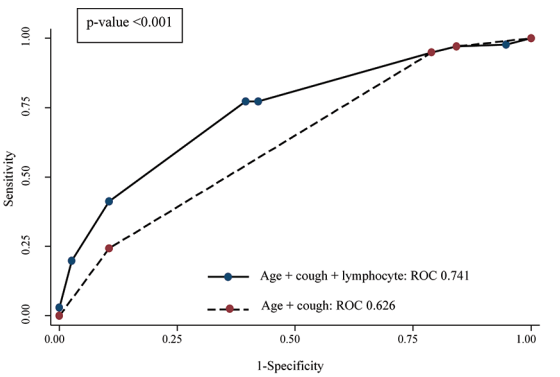

Figure 1. AuROC comparison between model 3 vs. 7 to predict for viral infection.

Table 4. Types of microorganisms detected by RP-24-26 (n=208)

Type	Microorganisms	n (%)
Virus	1. Rhinovirus A/B/C (HRV)	52 (25.0)
	2. Influenza virus total	28 (13.5)
	• Influenza A virus (FluA)	1 (0.5)
	• Influenza A H1N1	17 (8.2)
	• Influenza A H3N2	5 (2.4)
	• Influenza A unsubtype	0 (0.0)
	• Influenza B virus (FluB)	5 (2.4)
	3. Respiratory syncytial virus total	27 (13.0)
	• Respiratory syncytial virus A (RSV A)	10 (4.8)
	• Respiratory syncytial virus B (RSV B)	12 (5.8)
	4. Parainfluenza virus total	25 (12.0)
	• Parainfluenza virus1 (PIV1)	4 (1.9)
	• Parainfluenza virus2 (PIV2)	3 (1.4)
	• Parainfluenza virus3 (PIV3)	14 (6.7)
	• Parainfluenza virus4 (PIV4)	4 (1.9)
	5. Adenovirus (AdV)	23 (11.1)
	6. Enterovirus (HEV)	18 (8.6)
	7. Bocavirus 1/2/3/4 (HBoV)	16 (7.7)
	8. Metapneumovirus (MPV)	7 (3.4)
	9. Coronavirus NL63 (CoV NL63)	4 (1.9)
	10. Coronavirus OC43 (CoV OC43)	1 (0.5)
	11. Coronavirus 229E (CoV 229E)	0 (0.0)
Bacteria	1. *Haemophilus influenzae*	16 (7.7)
	2. *Streptococcus pneumoniae*	11 (5.3)
	3. *Bordetella pertussis* (BP)	2 (1.0)
	4. *Mycoplasma pneumoniae* (MP)	1 (0.5)
	5. *Legionella pneumophila* (LP)	0 (0.0)
	6. *Bordetella parapertussis* (BPP)	0 (0.0)
	7. *Chlamydophila pneumoniae* (CP) (CE0086)	0 (0.0)

cases of BP, and one case of MP (Table 4).

Discussion

General outcome

The present study found that the most common cause of severe pneumonia is virus, which is similar to other studies[1,2]. However, the PERCH Multi-Country Case-Control Study[19] from seven countries in Africa and Asia in 2014 revealed that *S. pneumoniae* was the most common bacteria isolated [19 (33.9%) of 56]. The etiology analysis estimated that viruses accounted for 61.4% (95% credible interval [CrI] 57.3 to 65.6) of causes, whereas bacteria accounted for 27.3% (23.3 to 31.6) and *Mycobacterium tuberculosis* for 5.9% (3.9 to 8.3). Viruses were less common (54.5%, 95% CrI 47.4 to 61.5 versus 68.0%, 62.7 to 72.7) and bacteria more common (33.7%, 27.2 to 40.8 versus 22.8%, 18.3 to 27.6) in very severe pneumonia cases than in severe cases. The present study had only 98 pneumonia cases, so that it may limit the generalizability to the Thai population as RSV had the greatest etiological fraction (31.1%, 95% CrI 28.4 to 34.2) of all pathogens, which is similar to the present study.

Clinical presentation and laboratory finding

Age 13 to 24 months and sore throat statistically significantly predicted co-infection in the present study. The reason may be that children at 13 to 24 months usually went to nursery, which is known to increase the opportunity to be infected by many pathogens. In addition, children at a younger age who can complain of symptoms like sore throat, means that symptoms are severe to indicate a chance of bacterial complications. According to age, patients with viral pneumonia compare with those with bacterial pneumonia were slightly younger in the present study (12 months versus 13 months), which is different from the study of Juvén et al[20] that found mean age of 33.6 versus 49.2 months.

In a multicenter population-based study that included 2,358 children younger than 18 years hospitalized with radiographic evidence of pneumonia, 95% had cough, 90% had fever, 75% had anorexia, 70% had dyspnea, and 55% had chest wall retractions(1). Cough, muscle pain, and platelet of less than 150,000 were statistically significant predictors of viral pneumonia in the present study. It is in concordance with the respiratory symptoms of AdV pneumonia, which are cough (99%), rhinorrhea (82%), and dyspnea (42%)[21]. Thrombocytopenia could be a valuable marker of in-hospital mortality in patients with respiratory failure due to H1N1 influenza in the ICU scenario[22]. Cough is a prominent symptom of viral pneumonia because the viral infection enhances the cough reflex. Viral pneumonia leads to inflammation and irritation of the airways, whereas bacterial pneumonia will also have increased mucous and purulent secretion irritating the airways further. Cough may not be a feature initially since the alveoli have few cough receptors. It begins when the products of infection irritate cough receptors in the airways.

Occult pneumonia was found in 5.3% of patients with fever and no lower respiratory tract findings, tachypnea, or respiratory distress. There is limited utility in obtaining a chest X-ray (CXR) in febrile

children without cough. The likelihood of pneumonia increased with longer duration of cough or fever or in the presence of leukocytosis[23].

The present study indicated that statistically significant variables to predict viral pneumonia, and co-infection were cough, and age 13 to 24 months and lymphocytes of 40.0% or more, respectively. Pneumonia patients with cough had 4.42 times more chances to have viral cause, which was the same direction with lymphocytes of 40.0% or more, which have 4.60 times more chances to be co-infected with both virus and bacteria, especially in the age group of 13 to 24 months compared with 1 to 12 months.

Lymphocyte of 40% or more predict co-infection of pneumonia may be due to BP in two cases. In typical pertussis in young infants, there is leukocytosis with lymphocytosis and apneic episodes[24]. Bacteria was found to be the cause of pneumonia in the present study for 12%.The most common bacteria were *H. influenzae* found in 16 cases (7.7%) and *S. pneumoniae* in 11 cases (5.3%). In the present study, two cases of BP infections were found, who were a one month old and a four months old, and had not yet been vaccinated. MP was found in only one case. *H. influenzae* and *S. pneumoniae* are still common causes of bacterial pneumonia in children. Nevertheless, Thai children should be encouraged to receive vaccines against both *H. influenzae* and *S. pneumoniae*. Hib vaccine is now included in the EPI program for Thai children. *H. influenzae* and influenza are the most common vaccine-preventable diseases in children.

Treatment

The recommendations of most guidelines are based on in vitro susceptibilities of the most likely pathogen or pathogens, rather than evidence of the superiority of one antibiotic over another. Clinical response to empiric therapy and results of microbiologic studies, when available, help to determine whether additional evaluation or changes in therapy are necessary[25].

In sole viral pneumonia case, 79.8% received antiviral drug, 74.6% had antibiotic. The authors' hospital also has a rapid test for influenza, which will confirm the positive results. However, in severe pneumonia and high-risk group, antiviral drugs and antibiotic therapies are often given as empirical treatment. Because the authors found 12% of co-infection in severe pneumonia cases, early initiation of antimicrobial agents in patient age 13 to 24 months should be recommended and antibiotic continually used until clinical improve or known result of PCR test. PCR tests in a clinical setting would help doctor to faster de-escalate the antimicrobials.

Limitation

The present study had some limitation. First, the study was done only in severe pneumonia disease, not all cases of pneumonia in children. Second, the selection bias cannot be ruled out due to cases sent for a test between RP-24-26 were dependent on the doctor. Third, RP-24 result is reported in two to three days while the RP-26 takes about one week, which does not help the doctor's decision to treat in the first two to three days. Fourth, because RP-26 helps detect *S. pneumoniae* and *H. influenzae*, which RP-24 does not, this may cause information bias. Fifth, the numbers of only bacteria infected children were small in the present study. The authors combined bacteria with co-infection of virus and bacteria to increase the power of analysis. To differentiate between bacterial alone and viral infection, more sample will be needed in the future study. However, the MI analysis that was performed in variables that contained over 10% of missing values such as muscle pain, platelet count, ensures the final model by giving the same results with a slightly different effect from the complete case analysis. Therefore, the authors reported results from a complete dataset. Last, the infection may not be available in only 26 species. There are other infections not being examined, such as herpes and cytomegalovirus (CMV). As of today, RP-33 or more are available, which give chances to improve microorganism's detection.

Conclusion

Coughing is a predominant symptom for childhood pneumonia caused by virus. In addition, pneumonia patients age 13 to 24 months who have lymphocyte of more than 40% should start and continue antibiotics until complete course.

What is already known on this topic?

According to the previous evidence, no clinical or radiological characteristic was helpful in the separation among viral, bacteria, and atypical bacterial etiology of CAP in children. The proportion of patients with increased WBC or ESR, CRP did not differ between bacterial and viral pneumonias.

What this study adds?

This study found some potential clinical manifestations as predictors to differentiate viral and bacterial pneumonia. Pneumonia children with

cough had 4.42 times more changes to have viral cause. Furthermore, children with lymphocytes of 40.0% or more have 4.60 times more chance to be co-infected with both virus and bacteria, especially in an age group 13 to 24 months compared with 1 to 12 months. The final model for viral pneumonia predictions, which are age group13 to 24 months and cough combined with lymphocytes of 40.0 or more, can correctly identified viral pneumonia for 74%.

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Conflicts of interest

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