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Several prognosis factors of severe pertussis in children treated at Vietnam National Children's Hospital (2019-2020)

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Abstract:

A prospective, descriptive study was conducted on 382 pediatric patients diagnosed with pertussis at Vietnam National Children's Hospital over a two-year period, from January 1st, 2019, to December 31st, 2020. Of all patients participating in this study, children with severe conditions accounted for 30.1% (115/382). Several factors were found to be associated with the risk of this condition with odds ratios (OR) and 95% confidence intervals (CI), including a decrease in the duration of the onset phase by 5 days [OR 1.53, 95% CI: 1.002-2.34], fever [2.49, 1.18-5.24], cyanosis [9.59, 2.9-31.7], pneumonia [14.45, 6.06-34.5], pulmonary hypertension [4.15, 1.02-16.83], an increase of 10 g/l in white blood cell (WBC) count in the full blood count (FBC) test [1.39, 1.05-1.84], a 5-cycle reduction in Cycle threshold (Ct) value in the pertussis real-time PCR test [1.36, 1.01-1.84], and superinfection [3.94, 1.84-8.48 times]. A WBC count in FBC of ≥30 g/l could be used as a prognostic factor for the risk of severe illness condition (sensitivity 46.1%, specificity 90.6%), the requirement for mechanical ventilation (sensitivity 57.1%, specificity 88.5%), and mortality (sensitivity 100%, specificity 91%).

Keywords: **children, severe pertussis, Vietnam National Children's Hospital.**

Classification number: **3.2**

1. Introduction

Pertussis is an acute respiratory tract infection caused by Bordetella pertussis. Despite the discovery of the pertussis vaccine nearly a century ago, the disease has never been completely under control. According to the World Health Organization (WHO) in (2019) [1], there were approximately 24.1 million annual cases of infection, resulting in 160,700 deaths among children under 5 years old, with infants accounting for 53% of the recorded deaths. Over the past three decades, reports from many countries have indicated the risk of pertussis outbreaks, even in countries with high vaccination coverage rates [2]. This re-emerging disease has posed significant challenges to the public health system [3]. Furthermore, the illness itself, along with severe disease conditions and intractable complications such as severe pneumonia and pulmonary hypertension, has placed a substantial burden on medical personnel [4, 5].

In Vietnam, pertussis has not been completely controlled. In fact, since 2015, the number of pertussis cases has been steadily increasing [6-8]. The fatality rate of pertussis in the inpatient population is estimated to be around 1.5-2.8% [9-11], with deaths predominantly occurring in infants under 3 months of age [9, 10]. Identifying risk factors for severe conditions helps clinicians accurately prognose each patient, enabling timely intervention and reducing the risk of fatal outcomes. Considering these factors, the primary objective of this study is to "Identify prognostic factors of severe pertussis in children treated at Vietnam National Children's Hospital (2019-2020)".

2. Participants and method

2.1. Participants

The study included paediatric patients under 16 years old who were diagnosed with pertussis and received treatment at the National Children's Hospital between January 1st, 2019, and December 31st, 2020.

The diagnosis of pertussis was based on the criteria outlined by the Global Pertussis Initiative 2011 (GPI 2011) and a positive pertussis real-time PCR test.

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Exclusion criteria: Participants whose parents or caregivers did not consent to participate in the study.

2.2. Method

Study design: This was a prospective descriptive study of a case series.

Sampling method: Convenience sampling was employed to collect a sample size of 382 pediatric patients.

Severe pertussis was defined as follows: Children with respiratory failure requiring continuous oxygen supplementation for at least 24 hours (excluding cases where children only required oxygen support during paroxysmal coughing episodes and stable children without oxygen needs outside of coughing episodes), children requiring endotracheal intubation and mechanical ventilation, and/or children with circulatory collapse and multiorgan failure necessitating additional resuscitation measures such as blood transfusion, dialysis, or extracorporeal membrane oxygenation (ECMO).

Processed software: The data were processed using SPSS 22.0, a statistical software.

Ethical considerations: The study received approval from the Medical Ethics Committee of the Vietnam National Children's Hospital and the National Institute of Malariology, Parasitology, and Entomology.

3. Results

3.1. Rate of severe disease

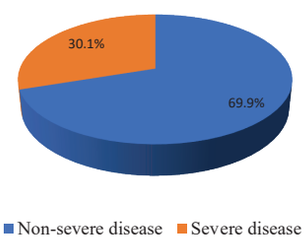

Fig. 1. Severe disease rate.

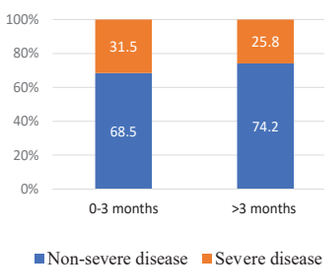

Fig. 2. Severe disease rate by age group.

The rate of children with severe pertussis was 30.1% (115/382) (Fig. 1), with infants aged 0-3 months accounting for 31.5% (91/289). In the group of children over 3 months old, the rate was 25.8% (24/93) (Fig. 2). However, this difference was not statistically significant (p=0.3>0.05).

3.2. Factors associated with severe disease conditions

Relationships between epidemiological characteristics and severe disease: Physiological factors such as preterm birth, malnutrition, underlying medical conditions, and lack of pertussis vaccination are likely to increase the risk of severe illness by 2.5 (95% CI: 1.1-5.6), 6.6 (95% CI: 1.7-25.3), 2.7 (95% CI: 1.3-5.7), and 3.3 (95% CI: 1.4-7.5) times, respectively (Table 1).

Table 1. The relationship between epidemiological characteristics and severe disease.

Features	Severe disease (n=115)		Non-severe disease (n=267)		p	OR (95% CI)
	Number	*%*	*Number*	*%*		
Premature birth	13	11.3	13	4.9	0.026	2.5 (1.1-5.6)
Malnutrition	8	7.0	3	1.1	0.04	6.6 (1.7-25.3)
Base diseases	16	13.9	15	5.6	0.008	2.7 (1.3-5.7)
No pertussis vaccination	108	93.9	220	82.4	0.005	3.3 (1.4-7.5)

Clinical symptoms and complications: Table 2 demonstrates that symptoms of fever, cyanotic cough, apnoea, convulsions, and complications of pneumonia and pulmonary arterial hypertension are associated with an increased risk of severe pertussis (p<0.01).

Table 2. Symptoms and complications associated with severe disease.

Symptom	Severe disease (n=115)		Non-severe disease (n=267)		p	OR (95% CI)
	Number	*%*	*Number*	*%*		
Fever	50	43.5	61	22.8	<0.001	2.6 (1.6-4.1)
Stridor	7	6.1	16	6.0	0.9	
Cyanotic cough	110	95.7	157	58.8	<0.001	15.4 (6.1-39.0)
Apnoea	29	27.8	13	4.9	<0.001	6.6 (3.3-13.2)
Convulsion	15	13.0	2	0.7	<0.001	19.9 (4.5-88.5)
Pneumonia	107	93.0	79	29.6	<0.001	31.8 (14.8-68.4)
Pulmonary arterial hypertension	30	26.1	7	2.6	<0.001	13.1 (5.6-30.9)

Subclinical signs: Table 3 presents a comparison of average leukocyte count, lymphocyte count, neutrophil count, platelet count, and CRP levels between children with severe and non-severe disease, which revealed significantly higher values in the severe disease group (p<0.01). Thus, these results indicate that an increase in these indicators is associated with the severity of the disease in children.

Table 3. Complete blood count and indicators related to severe disease.

Indicator	Severe disease (n=115)		Non-severe disease (n=267)		p
	$\bar{x}$	*SD*	$\bar{x}$	*SD*	
WBC(G/1)	28.6	19.1	17.1	8.9	<0.001
Lym. (G/1)	16.3	9.9	11.9	6.9	<0.001
Neut (G/1)	8.4	7.7	3.4	2.7	<0.001
PLT (G/1)	507.9	181.0	457.4	153.2	0.006
CRP (mg/l)	13.4	30.3	2.5	9.1	<0.001
Ct (cycle threshold)	23.8	6.2	26.1	5.9	0.001

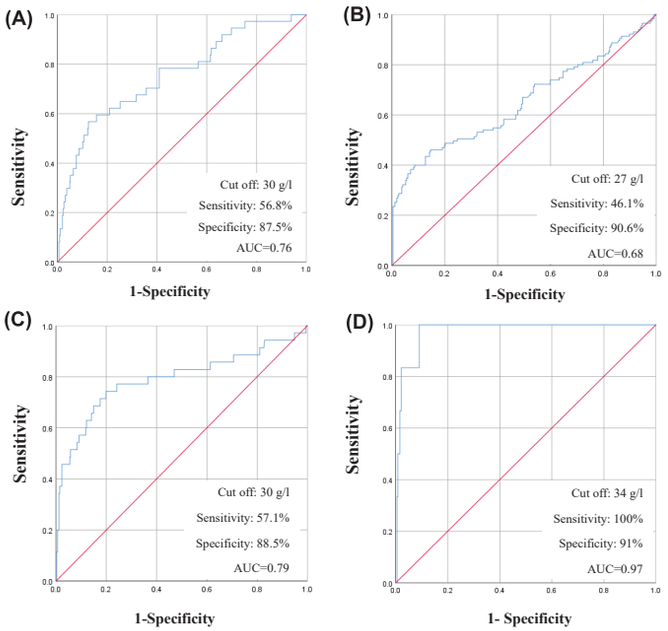

Fig. 3. The ROC curve of the white blood cell count predicting. (A) The risk of pulmonary hypertension; **(B)** The risk of severe disease; **(C)** The risk of mechanical ventilation; **(D)** The risk of death. Note: Cut off: cut point; AUC: area under the curve.

The peripheral blood total leukocyte count has demonstrated predictive value for pulmonary hypertension, severe disease, mechanical ventilation, and mortality in children with pertussis (Fig. 3): An increase in white blood cell count of more than 30 g/l was found to predict the risk of developing pulmonary hypertension, with a sensitivity of 56.8% and specificity of 87.5%. A white blood cell count of ≥27 g/l could predict the risk of severe pertussis, with a sensitivity of 46.1% and specificity of 90.6%. A white blood cell count of ≥30 g/l was shown to predict the risk of requiring mechanical ventilation, with a sensitivity of 57.1% and specificity of 88.5%. A white blood cell count of ≥34 g/l was identified as a predictor for mortality due to pertussis, with a sensitivity of 100% and specificity of 91%.

Table 4. Cycle threshold (Ct) values associated with the complications of pulmonary hypertension, severe illness, risk of mechanical ventilation, and mortality.

Ct value/(-5)		B	p	OR (95% CI)
pH	Ct/(-5)	0.723	<0.001	2.06 (1.47-2.88)
Severe disease	Ct/(-5)	0.326	0.001	1.39 (1.15-1.67)
Mechanical ventilation	Ct/(-5)	0.628	<0.001	1.87 (1.35-2.61)
Mortality	Ct/(-5)	0.578	0.134	

Table 4 demonstrates that a low Ct value is associated with an elevated risk of complications, including increased pulmonary arterial pressure, severe pertussis, and the need for mechanical ventilation (p<0.01). Specifically, a 5-cycle reduction in Ct value is associated with: A 2.06-fold increase in the risk of elevated pulmonary arterial pressure (95% CI: 1.47-2.88). A 1.39-fold increase in the risk of severe pertussis (95% CI: 1.15-1.67). A 1.87-fold increase in the risk of requiring mechanical ventilation (95% CI: 1.35-2.61).

Table 5. Other tests.

Indicator	Severe disease			Non-Severe disease			p
	Quantity	$\bar{x}$	*SD*	*Quantity*	$\bar{x}$	*SD*	
Glucose (mmol/l)	79	5.5	1.2	31	5.7	1.1	0.65
NT-proBNP (pmol/l)	39	1373.0	2819.6	15	217.0	552.7	0.019
Troponin(ng/ml)	15	0.236	0.642	11	0.018	0.018	0.20

Table 5 reveals that the average NT-proBNP value in the severe group was 1373.0 pmol/l, whereas in the non-severe group, it was 217 pmol/l. This disparity was statistically significant (p<0.05). Conversely, the average serum glucose and troponin concentrations did not differ significantly between the severe and non-severe groups (p>0.05).

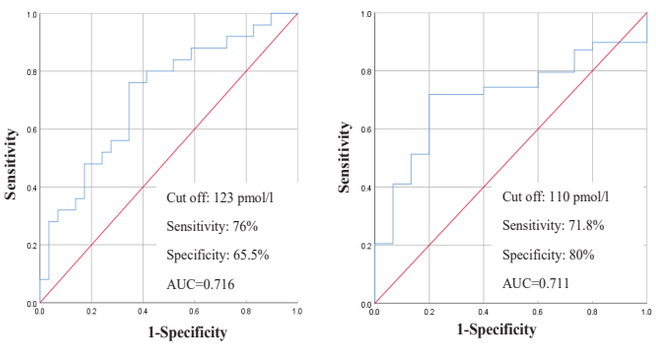

Fig. 4. ROC curve of NT-proBNP serum concentration predicting the risk of pulmonary arterial hypertension complications and severe disease.

The optimal cutoff point of NT-proBNP serum concentration for predicting the risk of pulmonary arterial hypertension in children with pertussis was found to be 123 pmol/l, yielding a sensitivity of 76% and specificity of 65.5%. The area under the ROC curve was 0.716 (95% CI 0.578-0.854). Similarly, the optimal cutoff point of NT-proBNP serum concentration for predicting the risk of severe pertussis was determined to be 110 pmol/l, with a sensitivity of 71.8% and specificity of 80%. The area under the ROC curve was 0.711 (95% CI 0.568-0.854) (Fig. 4).

Superinfection with other microorganisms: Based on the findings presented in Table 6, the proportion of pertussis-infected children with superinfection in the severe disease group was 43.5% (50/115), which was significantly higher than the non-severe disease group, which recorded a rate of 15,0% (40/267) with p<0.01.

Table 6. Superinfection associated with severe disease.

	Severe disease (n=115)	Non-severe disease (n=267)	p	OR (95% CI)
Superinfection	50 (43.5%)	40 (15.0%)	<0.001	4.4 (2.7-7.2)
Non-superinfection	65 (56.5%)	227 (85.0%)		

Determining prognostic factors for the disease through multivariate regression analysis: Multivariable logistic regression analysis revealed the following factors to be associated with severe disease status, with their respective odds ratios (OR) and 95% confidence intervals (CI): Time from onset of symptoms/(-5): [1.53, 1.002-2.34]; Presence of fever: [2.5, 1.18-5.24]; Cyanosis: [9.59, 2.9-31.7]; Pneumonia: [14.45, 6.06-34.5]; Elevated mean pulmonary arterial pressure: [4.15, 1.02-16.83]; Increase of 10 g/l in leukocyte count: [1.4, 1.05-1.84]; Decreased Ct value in Real-time PCR pertussis: [1.36, 1.01-1.84]; Superinfection with other microorganisms: [3.94, 1.84-8.48] (Table 7).

Table 7. Multivariate logistic regression analysis of prognostic factors for severe disease.

Associated factors	B	p	OR (95% CI)
Age (months)	0.027	0.096	1.03 (0.99-1.06)
Onset time/(-5)	0.43	0.049	1.53 (1.002-2.34)
Fever	0.91	0.017	2.49 (1.18-5.24)
Cyanosis	2.26	0.000	9.59 (2.90-31.70)
Apnoea	0.72	0.18	2.05 (0.73-5.78)
Pneumonia	2.67	0.000	14.45 (6.06-34.50)
Pulmonary hypertension	1.42	0.047	4.15 (1.02-16.83)
Leukocytes/(10)	0.33	0.023	1.390 (1.05-1.84)
Ct/(-5)	0.31	0.045	1.36 (1.01-1.84)
Superinfection	1.37	0.000	3.94 (1.84-8.48)

4. Discussion

According to the analysis of the correlation between various epidemiological and clinical characteristics with severe pertussis (as presented in Tables 1 and 2), certain factors stood out as being associated with an increased risk of severe pertussis. These factors included premature birth (gestational age <37 weeks), the presence of underlying diseases, and lack of pertussis vaccination. Additionally, children exhibiting symptoms such as fever, cyanosis, apnoea, seizures, or complications such as pneumonia and pulmonary hypertension were found to be at higher risk of developing severe pertussis.

Laboratory indicators, as shown in Table 3, including total leukocyte count, lymphocyte count, neutrophil count, platelet count, and CRP value, were found to be higher in the severe group compared to the non-severe group, suggesting a correlation between these indicators and the severity of the disease.

By analysing the ROC curve (as shown in Fig. 3), we determined that a white blood cell count of 27 g/l could predict the risk of severe disease with a sensitivity of 46.1% and specificity of 90.6% (AUC 0.68, 95% CI 0.62-0.74). A white blood cell count of 30 g/l could predict the risk of pulmonary arterial hypertension with a sensitivity of 56.8% and specificity of 87.5% (AUC 0.76, 95% CI 0.67-0.84), as well as the risk of requiring mechanical ventilation with a sensitivity of 57.1% and specificity of 88.5% (AUC 0.79, 95% CI 0.69-0.89). Notably, a white blood cell count of 34 g/l could predict the risk of death due to severe respiratory failure with a sensitivity of 100% and specificity of 91% (AUC 0.97, 95% CI 0.94-1). These results align with a study conducted by Tran Minh Dien (2015) [9] on the prognostic factor of severe respiratory failure, which found a significant association between a total blood white blood cell count ≥30.0 g/l and severe illness (OR: 4.1, 95% CI: 2.44-17.25). Similarly, F. Palvo, et al. (2017) [6] reported that an elevated white blood cell count of ≥30,000/mm^3 was associated with severe illness, and they established a cutoff value of 41.2 g/l for predicting the risk of ICU admission with a sensitivity of 64.7% and specificity of 89.5% (AUC 0.75, 95% CI 0.59-0.90). They also found a sensitivity of 100% and specificity of 81.6% in predicting the risk of death (AUC 0.93, 95% CI 0.84-0.98).

Therefore, our study results demonstrate a correlation between white blood cell count and complications such as pulmonary hypertension, severe illness, and death due to pertussis. A white blood cell count of ≥30 g/l has significant prognostic value for severe pertussis. Moreover, a low Ct value in pertussis real-time PCR testing was associated with an increased risk of pulmonary hypertension, severe illness, and the need for mechanical ventilation ($p<0.01$), as indicated in Table 4. This could be explained by the hypothesis that a low Ct value corresponds to a high bacterial load (per unit of the specimen) and an increased concentration of bacterial toxins (in serum or body tissue), thus increasing the risk of severe complications, illness severity, and the need for mechanical ventilation The association between Ct value and severe pertussis has been reported in previous study of R.A. Lewis, et al. (2020) [12]. Additionally, superinfection with other microorganisms was found to increase the risk of severe disease in children, as shown in Table 6.

Another indicator, NT-proBNP, was also found to be associated with severe disease (Table 6). Fig. 4 demonstrates that NT-proBNP levels can contribute to the prediction of the risk of pulmonary hypertension (with a cutoff value of 123 pmol/l, sensitivity of 76%, and specificity of 65.5%) and severe pertussis (with a cutoff value of 110 pmol/l, sensitivity of 71.8%, and specificity of 80%). Although the association between NT-proBNP and pulmonary hypertension has been reported by previous authors [13, 14], the association of NT-proBNP with severe pertussis has received little recognition.

Multivariate logistic regression analysis of factors associated with severe pertussis (Table 7) revealed that a shorter duration of disease onset, symptoms of fever and cyanosis, presence of pneumonia, pulmonary hypertension, elevated white blood cell count, low Ct value, and superinfection with other pathogens were closely associated with severe pertussis.

Previous studies by Tran Minh Dien (2015) [9] identified age (infants ≤3 months old), pneumonia, and peripheral blood leukocyte count ≥30.0 g/l as prognostic factors for severe pertussis (OR: 4.1, 95% CI: 2.44-17.25). C. Liu, et al. (2020) [14] recognised apnoea, elevated white blood cell count, and pulmonary hypertension as key determinants related to severe pertussis in infants under

120 days old. L. Kang, et al. (2022) [5] reported several factors related to severe disease, including age at onset, exposure history to individuals with pertussis, lack of pertussis vaccination, and symptoms such as paroxysmal cough, post-tussive vomiting, cyanotic or flushed face, and fever, which were more common in the severe disease group compared to the non-severe disease group. Furthermore, they found a higher percentage of peripheral blood leukocyte count, CRP levels, and pneumonia complications in the severe disease group.

Therefore, our study's findings align with the trends observed in most previous studies, highlighting several key factors associated with severe pertussis, including fever, cyanosis, pneumonia complications, and an elevated white blood cell count. Additionally, our study investigated the correlation between the duration of infection onset and disease severity. Specifically, we found that if the onset duration was reduced by 5 days, the risk of severe illness would increase by 1.53 times. Notably, pulmonary arterial hypertension was identified as a severe complication associated with an increased risk of severe illness, with 26.1% of children in the severe group and 2.6% in the non-severe group classified as having pulmonary arterial hypertension, and the difference between the groups was statistically significant. The pulmonary arterial hypertension group had a 4.15 times higher risk of severe disease compared to the non-pulmonary arterial hypertension group. The Ct value in the pertussis real-time PCR test was also found to be a factor associated with severe disease, as a 5-cycle reduction in the Ct value increased the risk of severe disease by 1.36 times (95% CI: 1.01-1.84). Furthermore, superinfection with other microorganisms increased the risk of severe disease by 3.94 times (95% CI: 1.84-8.48).

5. Conclusion

Our study revealed that 30.1% of children had severe pertussis, with infants aged ≤3 months accounting for approximately 31.5% of those cases. We identified several key factors associated with an elevated risk of severe pertussis, including a shorter duration of the onset phase, the presence of fever and paroxysmal cyanosis, complications such as pneumonia, elevated pulmonary artery pressure, an increased white blood cell count, a low Ct value on real-time PCR, and superinfection with other pathogens. Notably, a white blood cell count ≥30 g/l served as a significant indicator of an increased risk of pulmonary hypertension, severe illness, the need for mechanical ventilation, and fatality.

CRediT author statement

Do Thi Thuy Nga: Data collection, Conceptualisation, Methodology, Validation, Writing - Review and Editing; Nguyen Manh Cuong: Conceptualisation, Methodology, Validation, Writing; Phung Thi Bich Thuy: Writing - Review and Editing; Tran Minh Dien: Review and Editing.

COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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