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Evaluation of Predictive Factors of Empyema in Children with Parapneumonic Pleural Effusion

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Abstract

Background

Empyema is a complication of bacterial pneumonia which has a particular importance due to its significant morbidity and mortality in children. The aim of this study was to investigate the prognostic factors of empyema in children with parapneumonic pleural effusion.

Materials and Methods: This retrospective cross-sectional study investigated all patients under 14 years old with parapneumonic pleural effusion associated with community-acquired pneumonia (CAP) who were hospitalized in Tabriz Children's Hospital, Tabriz, Iran, between March 2016 and March 2020 (4 years). Demographic and clinical characteristics were collected via medical records of patients and assessed as possible factors for empyema. These included: pre-treatments with ibuprofen, antibiotic therapy before admission, duration of the disease, underling diseases, fever, tachycardia, tachypnea, and also some paraclinical variables such as leukocytosis, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), acidosis, blood, and pleural fluid culture results.

Results: Empyema associated with parapneumonic pleural effusion was detected in 47 patients (41.2%) of 114 hospitalized children. Based on logistic regression modeling, ibuprofen consumption history (OR = 7.16; 95% CI: 1.35-37.80; p = 0.02), tachypnea (OR = 17.13; 95% CI: 1.63- 179.90; p = 0.01), and leukocytosis (OR= 5.66; 95% CI: 2.10-15.24; p = 0.003) had a significant relationship with empyema occurrence.

Conclusion

Based on the findings of this study, the history of ibuprofen use, tachypnea, and leukocytosis were predictive factors for empyema in children with parapneumonic pleural effusion as a result of community-acquired pneumonia.

Key Words: Children, Empyema, Parapneumonic pleural effusion, Pneumonia.

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1- INTRODUCTION

According to radiological evidence, patients with pneumonia are divided into two groups: either with or without pleural effusion. Patients with pneumonia and pleural effusion are also divided into two subgroups based on biochemical and microbiological analysis of pleural fluid as well as macroscopic criteria: either with uncomplicated parapneumonic effusion or with complicated parapneumonic effusion. The second subgroup, which has the acute condition of effusion of pleura, is called empyema (1). As a complication of bacterial pneumonia, empyema is now a controversial topic in the field of research related to respiratory-lung diseases due to its significant morbidity and mortality in children (2, 3). The prevalence of empyema in adults is 5% in patients with pneumonia (4) and 0.6% for children (5, 6), and its prevalence is significantly increasing worldwide (7, 8).

The importance of this classification is in adopting an appropriate therapeutic strategy for the clinical management of pneumonia with pleural effusion. So, in cases with uncomplicated parapneumonic effusion, the disease can be controlled by prescribing antibiotics. But in the case of the complicated type (empyema), invasive interventions such as pleural drainage (9, 10) or video-assisted thoracoscopic surgery (VATS) are required (11). If these invasive interventions in empyema are not performed in a timely and correct manner, the disease can become associated with serious clinical and mortal complications. Therefore, a timely assessment of the severity of the disease is essential for the optimal management of empyema. On the other hand, invasive methods such as pleural drainage and VATS are associated with high risks and side effects (12, 13); therefore, the importance of prognosis to prevent financial burden and non-use of invasive treatments in uncomplicated cases becomes more apparent. As there are no specific criteria for this prediction, this study aimed to identify the predictive factors of empyema in children with parapneumonic pleural effusion to determine the clinical and laboratory criteria to differentiate mild and acute cases (empyema) to use minimally invasive methods and most efficient treatment strategies. Identification of possible prognostic factors can decrease morbidity and mortality in children with empyema and the length of their hospital stay.

2- MATERIALS AND METHODS

2-1. Study design, setting and Patient Population

Our descriptive-retrospective cross-sectional study was conducted at the Children's Specialized Hospital in Tabriz, Iran. The study began after the approval of the Ethics Committee of Tabriz University of Medical Sciences (ID-code: IR.TBZMED.REC.1398.RRC).

The principles of data confidentiality based on the Helsinki statement were observed. The medical records of all the patients under 14 years who were hospitalized with a diagnosis of bacterial pneumonia, pleural effusion, and empyema between March, 2020 and March, 2020 were examined. Patients with community-acquired pneumonia (CAP) who had focal infiltrates in chest X-ray and were diagnosed with pleural effusion were entered into the study.

The patients were excluded if the cause of pneumonia was nosocomial, aspiration, cystic fibrosis, or of a viral origin. The patients were divided into two groups based on biochemical and microbiological analyses of pleural fluid and macroscopic evidence; one with uncomplicated parapneumonic effusions and one with complicated parapneumonic effusions (empyema). The criteria for the diagnosis of complicated parapneumonic effusions (empyema) were pleural effusion with

macroscopic presence of pus, a positive gram stain or culture of pleural fluid, a pleural fluid pH under 7.2 with normal peripheral blood pH, lactate dehydrogenase (LDH)>1000 IU/mL, and glucose < 60 mg/dL (13).

2-2. Data collection

The general data included: baseline characteristics, height, weight, history of an underlying disease, pre-hospital antibiotic therapy and pre-hospital ibuprofen use, duration of illness, vital signs at admission, and having risk factors of aspiration. The laboratory data included: the number of white blood cells, platelets, neutrophils, acidosis, serum albumin, serum levels of acute phase proteins (CRP), erythrocyte sedimentation rate (ESR), and serum Na level measured at admission, blood culture results and pleural fluid culture were collected using a checklist which was compiled by a pediatrician from the patients' medical records.

2-3. Data Analysis

All statistical analyses were conducted in SPSS software version 22.0. Qualitative (categorized) variables were summarized by frequency (percentage). Quantitative variables with normal distribution were summarized by mean (standard deviation), and for summarize of Quantitative variables without normal distribution we used median and interquartile range (IQR). The possible relationship between empyema occurrence and each of quantitative and qualitative variables was examined by independent T test and Chi-square tests, respectively. Finally, in order to control the effect of potential confounders, significant variables in univariate analysis were entered in a logistic regression model and the results were reported by the odds ratio (OR), and its corresponding 95% confidence interval (CI). P-value less than 0.05 was considered a significant level.

3- RESULTS

In the present study, 114 medical records related to children admitted to Children's Hospital of Tabriz, Iran, in a period of 4 years (March 2016 to March 2020) who suffered from parapneumonic pleural effusion following community-acquired pneumonia (CAP) were investigated. Fifty-five (48.2%), and 59 (51.8%) of these patients were boys and girls, respectively. Mean and standard deviation age of study participants were 37.9 ±17.9 months with the range of 1 to 166 months. Empyema was diagnosed in 47 people (41.2%). The baseline and clinical characteristics of children with parapneumonic effusions (Empyema), and without empyema are summarized in **Table. 1**.

The findings showed that there was no significant statistical difference between the two groups in terms of age (P = 0.80), and gender (P= 0.79). The history of ibuprofen and tachypnea varies significantly between two groups of children (with and without empyema), so that children with a history of ibuprofen (P <0.001), and children with tachypnea (P <0.001) were more likely to have empyema. No significant difference was observed between the two groups in comparing other factors such as weight, height, history of underlying disease, fever (temperature >38.0 °C) on admission, underlying disease, antibiotic therapy before admission, having risk factors for aspiration and duration of the disease (P>0.05).

Table-1: Comparison of baseline and clinical characteristics in children with or without empyema because of parapneumonic pleural effusion.

Variables		Outcome		P-value
		Non- empyema (n =67)	Empyema (n =47)	
Age (month), Median ± IQR		36.0±48.0	36.0±48.0	0.80¥
Gender	Female	34 (57.6%)	25 (42.4%)	0.79
	Male	33 (60.0%)	22 (40.0%)	
Weight (Kg)		18.39 ±11.27	18.07±7.96	0.80¥
Height (Cm)		102.40±25.58	102.40± 22.08	>0.99¥
Tachycardia	Yes	43 (53.8%)	37 (46.3%)	0. 1
	No	24 (70.6%)	10 (29.4%)	
Tachypnea	Yes	28 (54.9%)	23 (45.1%)	<0.001
	No	39 (61.9%)	24 (38.1%)	
Fever (temperature >38.0 °C) on admission	Yes	28 (54.9%)	23 (45.1%)	0.4
	No	39 (61.9%)	24 (38.1%)	
Underlying diseases	Yes	26 (68.4%)	12 (31.6%)	0.16
	No	41(53.9%)	35 (46.1%)	
Pre-treatments with ibuprofen	Yes	9 (30.0%)	21 (70.0%)	<0.001
	No	58 (69.0%)	26 (31.0%)	
Antibiotic therapy before admission	Yes	35(57.4%)	26 (42.6%)	0.74
	No	32 (60.4%)	21 (39.6%)	
Risk factors for aspiration	Yes	6 (46.2%)	7 (53.8%)	0.3
	No	61 (60.4%)	40 (39.6%)	
Duration of the disease (day)*	1-7	28 (62.2%)	17 (37.8%)	0.5
	7-14	22 (57.9%)	16 (42.1%)	
	>14	11 (47.8%)	12 (52.2%)	

Continuous variables presented as Median (IQR) and Categorical variables are presented as counts (%).
¥ Mann-Whitney U test was used for analysis.
 Chi-square test was used for analysis.
*Information of disuses' duration for eight cases were missed. IQR: interquartile range.

Mean and standard deviation of age in studied children were 50.83±37.32 and 50.83±37.32 months, respectively.

Comparison of paraclinical laboratory parameters measured in the studied children showed that there is a significant statistical relationship between occurrence of empyema and some paraclinical measures such as leukocytosis (WBC> 15000 µl) (P <0.001), neutrophilia > 12000 µl (P= 0.001), Thrombocythemia (platelet= 450000 µl) (P < 0.001), hypoalbuminemia (Alb <3 g/dL) (P = 0.006), high ESR (P=0.005), and positive blood culture (P=0.04) (**Table. 2**).

Table-2: Laboratory data associated with the empyema in children with parapneumonic pleural effusion.

Variables		Non- empyema (n =67)	Empyema (n =47)	P- value
WBC > 15000 µl	Yes	18 (38.3%)	29 (61.7%)	<0.001
	No	49 (73.1%)	) 18 (26.9%)	
Neutrophils > 12000 µl	Yes	12 (35.3%)	22 (64.7%)	0.001
	No	55 (68.7%)	25 (31.3%)	
Platelet > 450000 µl	Yes	16 (39.0%)	25 (61.0%)	0.001
	No	51 (69.9%)	22 (30.1%)	
CRP	Negative	22 (61.1%)	14 (38.9%)	0.4
	1+	27 (65.9%)	14 (34.1%)	
	2+	14 (50.0%)	14 (50.0%)	
	3+	4 (44.4%)	5 (55.6%)	
Acidose	Yes	4 (100.0%)	0	0.08
	No	54 (55.1%)	44(44.9%)	
Albumin < 3 g/dL	Yes	9 (37.5%)	15 (62.5%)	0.006
	No	25 (73.5%)	9 (26.5%)	
Na <135 mmol/L	Yes	6 (37.5%)	10 (62.5%)	0.1
	No	47 (59.5%)	32 (40.5%)	
ESR	< 50 mm/hr	22 (84.6%)	4 (15.4%)	0.005
	50-75 mm/hr	9 (60.0%)	6 (40.0%)	
	75-100 mm/hr	14 (66.7%)	7 (33.3%)	
	> 100 mm/hr	21 (42.9%)	28 (57.1%)	
Blood Culture	Positive	3 (30.0%)	7 (70.0%)	0.04
	Negative	64 (62.1%)	39 (37.9%)	
Pleural fluid culture	Positive	0	3 (100.0%)	0.13
	Negative	63 (57.3%)	47 (42.7%)	

Chi-square test and fisher exact test were used for analysis. *WBC: white blood cells; CRP: C-reactive protein; NA: Sodium; ESR: Erythrocyte Sedimentation Rate, **Chi-square test and fisher exact test were used for analysis.

The results of multivariate logistic regression modeling showed that the history of ibuprofen consumption increased the chance of empyema in children with parapneumonic pleural effusion by about 7 times (OR = 7.16; 95% CI: 1.35 to 37.80; P = 0.02). Also, having the symptoms of tachycardia (OR = 17.13; 95% CI: 1.63 to 179.90; P = 0.01), and leukocytosis (OR = 5.66; 95% CI: 2.10 to 15.24; P= 0.003) increases the empyema incidence (**Table. 3**).

Table-3: The results of the multivariate logistic regression analysis on the Predictive factors associated with empyema in children with parapneumonic pleural effusion.

Variables	Odds Ration	95% CI	P-value
Pre-treatments with ibuprofen	7.16	1.35 – 37.80	0.02
Tachypnea	17.13	1.63 – 179.90	0.01
WBC>15000	5.66	2.10 – 15.24	0.003

WBC: white blood cells, CI: confidence interval.

4- DISCUSSION

Given the significant mortality of empyema in children and the need for prompt and timely detection to better manage this complication, it is necessary to identify the criteria for predicting the severity of pneumonia in children. The aim of this study was to identify and predict empyema prognostic factors in children with CAP-induced pleural effusion based on their medical records. Different outcomes such as fever duration score (14), mean hospital stay, thoracoscope (15), blood or pleural fluid culture, and factors related to blood cell counts are examined in such studies. In our study, the history of drug use, the clinical status of the children before admission, counting of blood cells and pleural fluid culture during admission were investigated with the justification that in the early hours of admission these factors can be quickly measured and recorded. They are also can be the basis for predicting empyema in the shortest possible time, while checking some factors such as fever duration score is very time consuming. Findings of this study showed that children with parapneumonic pleural effusion are up to 7 times more likely to develop empyema if they have a history of ibuprofen use and up to 17 times more likely to have a history of tachypnea. The results of our study are consistent with those of Elemraid et al. In 2015, and Byington et al. In 2002, who reported that children with empyema had a significant history of ibuprofen use before hospitalization (8, 16). There are many theories, from simple to complex, about the reason for the relationship between the history of ibuprofen and empyema. A simple explanation for this connection is that children generally do not have a favorable general condition before the onset of empyema and are constantly involved in conditions such as high fever, so they use ibuprofen to temporarily relieve such conditions. A more complex relationship can be explained by the fact that high fever in diseases such as pneumonia has a regulatory mechanism in infection control so that many pneumococcal bacterial species have a temperature-sensitive property and die between 40 and 41 degrees (17, 18). On the other hand, having a fever above 38 degrees is a prerequisite for preventing the multiplication of bacteria and viruses and initiating the induction of many immune responses (19); therefore, taking ibuprofen

upsets this balance by lowering the fever and allows more remnants of pneumococcal species to survive. As a result, conditions are dramatically prepared for empyema occurrence (20). In our study, the disruption of these regulatory mechanisms of the fever process in the face of some conditions such as pneumonia due to pre-hospital ibuprofen use could be a reasonable justification for the association between pre-hospital ibuprofen use and empyema occurrence. In our experience, we found the statistical relationship between tachypnea and empyema.

To our knowledge, no study has been found that examines the relationship between tachypnea and empyema and this finding can be the new message of our results. Tachypnea is approximately the most important sign that can be seen and measured without any special method or device (compared to other factors such as blood cell count variables, pleural fluid and blood culture), and is very useful in predicting empyema. The possible reason could be a worsening of the pneumonia that is becoming empyema, as tachypnea is a specific evidence of the differentiation of simple pneumonia from the complex and acute condition of the complicated parapneumonic pleural effusion empyema (21). Consistent with our study, a multivariate analysis by Falguera et al. (2014) showed that leukocytosis is a prognostic factor of empyema (21). Ahmed and colleagues (2006) also showed that the occurrence of empyema has a significant relationship with leukocytosis and neutrophilia (22). The retrospective nature of this investigation and the impossibility of tracking the studied subjects are some of the limitations of our study. Another limitation was that the clinical records of patients during the admission to the hospital were not always available, as pleural effusion may occur during hospitalization.

5- CONCLUSION

Based on the findings of this study, a history of ibuprofen use, tachypnea, and leukocytosis are predictive factors for empyema in children with pleural effusion from community-acquired pneumonia (CAP). It is, therefore, helpful to design a scoring system to predict the incidence of empyema in patients with parapneumonic pleural effusion. This system can be used as a screening tool in children with empyema for an early intervention and finding the most effective and the least dangerous treatment strategy.

6- CONFLICT OF INTEREST: None.

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