RESEARCH ARTICLE / *Araştırma Makalesi*

The Relationship Between Laboratory Evaluations in The Separation of Viral and Bacterial Pneumonia in Children

Çocuklarda Viral ve Bakteriyel Pnömoniyi Ayırmada Laboratuvar Değerlendirmeleri Arasındaki İlişki

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Abstract

Objective	Basic infections of the lower respiratory tract (LRT) are bronchiolitis and pneumonia in children. The aim our study that determines the guiding laboratory parameters in discriminating between bacterial and viral LRT infections.
Materials and Methods	The patients who were diagnosed with LRT infection were divided into four groups based on the findings of chest radiography by radyologist in 2017. Their disease was classified as either viral or bacterial LRT infection in line with these findings. A correlation between chest radiography and laboratory findings was found by comparing c reactive protein (CRP), leukocyte, platelet, hematocrit, neutrophil, lymphocyte, neutrophil / lymphocyte and mean platelet volume (MPV) ratios using statistical methods.
Results	Of 344 patients included in the study, 43 patients with lober segmental, dense-patched and peribronchial infiltration and 301 patients with patched-peribronchial infiltration or normal radiography were evaluated as bacterial and viral according to the findings of chest radiography, respectively. We found a statistically significant difference in only CRP values between the viral and bacterial groups ($p = 0.034$).
Conclusion	It is seen that CRP supports the findings of chest radiography in discrimination of the bacterial cause in community-acquired LRT infections. In children, the elevation in CRP value can be a valuable indicator in supporting bacterial chest radiography finding and deciding to start empirically antibiotic treatment of pneumonia.
Keywords	antibiotic; bronchiolitis; c reactive protein; children; pneumonia

Öz

Amaç	*Alt solunum yolu (ASY)' nun temel enfeksiyonları; bronşiyolit ve pnömonidir. Çalışmamızdaki amacımız akciğer grafi bulgularına göre sınıflanmış viral-bakteriyel ASY enfeksiyonlarının ayırımında, labaratuvar değerlerinin önemini saptamaktır.*
Gereç ve Yöntemler	*Hastanemizde 2017 yılında, ASY enfeksiyonu tanısı almış hastalar, akciğer grafi bulgularına göre radyoloji uzmanı tarafındandört gruba ayrıldı ve bu bulgulara göre viral veya bakteriyel ASY enfeksiyonu olarak sınıflandı. Hastaların c reaktif protein (CRP), lökosit, trombosit, hematokrit, nötrofil, lenfosit, nötrofil/lenfosit ve ortalama trombosit hacmi oranları istatistik yöntemlerle karşılaştırılarak, akciğer grafisi ve labaratuvar bulguları arasında korelasyon istatistik yöntemlerle saptandı.*
Bulgular	*Çalışmaya dahil edilen 344 hastanın akciğer grafi bulgularına göre lober segmental ve yoğun yamalı ve peribronşiyal infiltrasyonu olan 43 adedi bakteriyel, yamalı-peribronşiyal infiltrasyonu olan veya grafileri normal bulunan 301 ASY enfeksiyonu viral olarak değerlendirildi. Viral ve bakteriyel grup arasında sadece CRP değerleri arasında istatistiksel fark bulduk ($p=.0,034$).*
Sonuç	*Toplumdan kazanılmış pnömonilerde, yatan hastalarda yaptığımız çalışmada, viral bakteriyel ASY enfeksiyonu ayırımında akciğer grafisi ile CRP nin arasında anlamlı ilişki görülmüştür. Çocuklarda, CRP değerindeki yükseklik, pnömoni tedavisinde ampirik antibiyotik başlama kararını vermede, akciğer grafisindeki bakteriyel bulguları destekleyen değerli bir göstergedir.*
Anahtar Kelimeler	*antibiyotik; bronşiyolit; c reaktif protein; çocuk; pnömoni*

INTRODUCTION

Pneumonia is one of the leading causes of child deaths in developing countries.[1] It is a common disease in the World, especially in children less than 5-years-old. Pneumonia is four times more common in developing countries than developed countries in children.[2-4]

Other one of the lower respiratory tract infection (LRTI) acute bronchiolitis (AB) is a clinical viral syndrome followed by the findings of upper respiratory tract infection (URTI) and usually seen in children under 2 years of age.[5] Reduction in mortality and morbidity is dependent on timely and accurate treatment of these infections.[6]

AB or pneumonia is diagnosed by clinical signs and findings. However, considering complications, chest radiography and laboratory examination, such as hemogram, C-reactive protein (CRP) or specific examinations for the detection of agent may be needed for the patients.1The CRP reaches high levels after 12 hours of tissue damage. Especially in acute invasive infections, the serum concentration is markedly increased in parallel with the inflammation severity. The CRP response is not agent-specific. It can be identified to be low for viral infections and high for acute bacterial infections.[7]

In addition to leukocyte counts analyzed with CRP, mean platelet volume (MPV) and neutrophil/lymphocyte ratio may also increase in acute infections. Recently, not only platelet counts but also MPV have been searched for some of the infectious and systemic diseases, and significant findings have been revealed.[8,9] It is not always possible to discriminate between viral and bacterial lower respiratory tract infections in children, so this fact may lead to unnecessary antibiotic use or delayed treatments.[1] There is no gold standard to define bacterial pneumonia and no point-of-care test to differentiate between viral and bacterial pneumonia. Determining the aetiology of pneumonia remains difficult in children who cannot produce good quality sputum for culture.[10]

It was aimed to investigate the correlation of chest radiography and laboratory values of leukocyte, CRP, neutrophil / lymphocyte ratio, platelet count and MPV values which were analyzed simultaneously during admission in discrimination between viral and bacterial lower respiratory tract infections.

MATERIALS and METHODS

In our retrospective cross-sectional descriptive type study, information of patients admitted to our pediatric clinic with the diagnosis of lower respiratory tract infection during hospitalization period from 01.01.2017 to 31.12.2017 were obtained from the Hospital Information Management System. This study was performed following approval from the Haseki Hospital ethical committee (The chair person: Dr Fuat Şar, No 584, Approval date: 21.11.2017). The chest radiography of the patients taken during hospitalization was evaluated by a radiologist who was not aware of their clinical and laboratory findings. Radiography findings about lungs were evaluated in 4 groups: 1. normal, 2. lobar segmental consolidation 3. patched consolidation 4. Peribronchial, perivascular, interstitial, reticular nodular density increase. In some patients the findings in groups 2 + 3 were seen together, while in some patients the findings in groups 3 + 4 were seen together. The preliminary diagnoses suggested by the radiologist based on the radiological findings were grouped as 1. Bronchiolitis, 2. Viral Pneumonia 3. Bacterial pneumonia and 4. Normal. The patients who were determined to have no findings of bronchiolitis or radiological findings according to the chest radiographyby radiologist were included in the viral-based group, because they were diagnosed with lower respiratory tract infection based on their physical examination.While the patients with lobar segmental consolidation in chest radiography were accepted to have bacterial pneumonia, other types of consolidations were evaluated as bacterial or viral based on the distribution of density.

The patients with severe immunodeficiency and the patients with infection other than lower respiratory tract

infection were excluded from the study. No viral examination was performed in our hospital. The patients who did not have the findings of fever and upper respiratory tract infection and the patients with a history of asthma or allergy were excluded as well.

Statistical methods

SPSS 15.0 for Windows program was used for statistical analysis. As part of descriptive statistics, number and percentage, and mean, standard deviation, minimum, maximum, and median were given for categorical variables and numerical variables, respectively. Student t test was performed in two independent groups whereas One Way Anova was performed in more than two groups when the comparisons of the numerical variables provided the normal distribution condition. When no normal distribution condition was provided, Mann Whitney U test and Kruskal Wallis test were applied. The ratios of categorical variables between groups were compared through the chi-square analysis.Thecorrelations between the numerical variables were examined by Spearman Correlation Analysis, since the parametric test condition was not met.Cut-off value was investigated with Roc Curve Analysis. Statistical (alpha) significance was accepted as $p < 0.05$.

RESULTS

In 2017, there were 417 patients who were hospitalized in the clinic for infants and older children and received treatment for lower respiratory tract infection. However, 59 patients who had pneumonia during hospitalization, were hospitalized 2 weeks prior to hospital admission and had neutropenia and immunocompromised or any additional infection, and 14 patients without simultaneous chest radiography and laboratory examinations were excluded from the study. 344 patients included in the study. Based on the evaluation of posteroanterior chest radiography taken during admission, 301 patients and 43 patients were evaluated as viral and bacterial pneumonia, respectively. There was no statistically significant difference in the mean age and gender of the children (p >0,05) (Table 1).

Table 1. Age and gender distributions of patientsin bacterial and viral lower respiratory tract infections groups according to chest x-ray findings

		Total		Viral lower respiratory tract infection(n=301 %87,2)		Bacterial lower respiratory tract infection (n=43 %12,5)		
		Ort.±SD	Min-Max (Median)	Ort.±SD	Min-Max (Median)	Ort.±SD	Min-Max (Median)	p
Age		9,1±10,0	0,5-48 (5,5)	9,0±10,1	0,5-48 (5,5)	10,0±9,5	1,5-48 (7)	0,138
		n	%	n	%	n	%	
Gender	Girl	148	43,0	127	42,2	21	48,8	0,410
	Boy	196	57,0	174	57,8	22	51,2	
(Number and percentage, and mean, standard deviation, minimum, maximum, and median-Sudent t test)								

Radiological evaluations of children with viral and bacterial lower respiratory tract are summarized in Table 2.

Table 2. Distribution of patients according to findings of chest X-ray imaging

	Viral lower respiratory tract infection		Bacterial lower respiratory tract infection		
Radiographical findings	n	%	n	%	P
Normal	215	71,5	0	0,0	<0,000
Lobar segmental consolidation	0	0,0	16	37,3	<0,000
Patchy consolidation	26	8,6	11	25,6	<0,010
Peribronchial perivascular interstitial reticular nodular density	49	16,3	2	4,6	<0,000
Lobar segmental+Patchy consolidation	0	0,0	5	11,6	<0,010
Patchy consolidation+ Peribronchial perivascular interstitial reticular nodular density	11	3,6	9	20,9	<0,010
(Number and percentage, and mean, standard deviation, minimum, maximum, and median- chi-square analysis)					

Among the evaluated parameters of the children with bacterial lower respiratory tract, only CRP level was significantly higher than that of the viral ones (p = 0.034).

No significant cut-off value was found in ROC curve at CRP level for viral - bacterial discrimination. ROC curve results for CRP are area 0,600 and asymptotic % 95 confidence interval 0,508-0,692 (Figure 1).

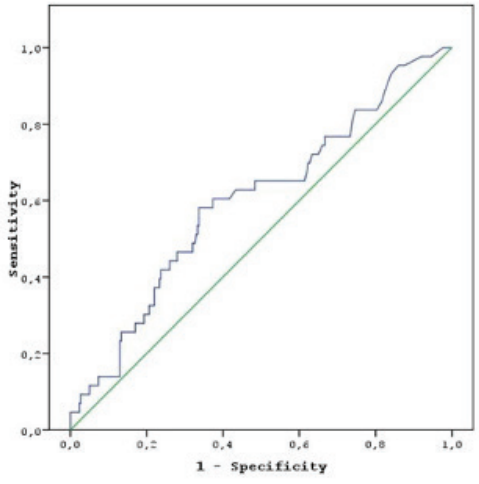

Figure 1: ROC analysis for c reactive protein

When we classified viral lower respiratory tract infections as with radiological findings and without radiological findings, we found a statistically significant difference between leukocyte mean values of the patients apart from CRP mean values (Table 3) (p = 0.015, p = 0.019, respectively).

Table 3. Comparison of variables by discriminating viral and bacterial groups according to presence of radiological findings

	Viral Lower Respiratory Tract Infection + Without Radiological finding		Viral Lower Respiratory Tract Infection + With Radiological finding		Bacterial Lower Respiratory Tract Infection		
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	p
Age (Year)	9,5±10,6	5,5	8,3±9,0	5,75	10,0±9,5	7	0,384
CRP[1]	17,2±27,7	7	18,1±27,3	8,2	31,5±57,2	13,4	**0,015**
Leukocyte	12,9±5,3	12,2	11,5±4,8	10,1	14,0±6,9	12,5	**0,019**
Hematocrit	31,6±3,2	31,6	31,3±3,2	31,45	31,5±3,6	30,9	0,848
Platelet	374,8±128,9	359	383,9±137,8	366,5	385,5±150,2	395	0,715
Neutrophil	45,0±28,1	39,6	38,4±19,4	34,6	48,0±23,3	39,4	0,122
Lymphocyte	45,4±20,8	48,7	50,0±17,1	52,35	42,3±21,1	46,7	0,169
MPV[2]	9,48±0,77	9,40	9,33±0,70	9,20	9,47±0,86	9,50	0,243
Neu/lymp[3]	2,12±3,23	0,83	1,30±2,09	0,67	2,25±2,93	0,86	0,119

1: C reactive protein 2: Mean platelet volume 3: Neutrophil/ Lymphocyte
(Number of mean, standard deviation, minimum, maximum, and median-One way Anova test)

When the whole group was taken into consideration, there was a significant difference only in CRP between the groups with viral and bacterial radiographic findings. Besides, there was a significant difference between CRP and leukocytes when viral group was classified according to the presence or absence of any finding. (p <0.05). During subgroup analysis, we found out that leukocyte value was significantly higher in patients without radiological findings than in patients with radiological findings (p = 0.031). Moreover, we revealed that leukocyte values of the bacterial lower respiratory tract infection group were significantly higher than those of the viral LRTI with radiological findings (p = 0.029). There was a statistically significant difference in CRP when we compared bacterial lower respiratory tract infection group to the viral lower respiratory tract infection group with or without radiological findings. Lastly, we detected statistically significant difference between viral lower respiratory tract infections with radiological findings and bacterial lower respiratory tract infections. (P <0.05) (Table 4).

Table 4. Statistical comparison of variables between subgroups

	Viral without radiological finding vs. Viral with radiological finding	Viral without radiological finding vs. Bacterial	Viral with radiological finding vs. Bacterial
	p	p	p
Age	0,809	0,216	0,168
CRP[1]	0,516	**0,037**	**0,048**
Leukocyte	**0,031**	0,495	**0,029**
Hematocrit	0,683	0,675	0,918
Platelet	0,523	0,528	0,890
Neutrophil	0,136	0,346	0,064
Lymphocyte	0,170	0,381	0,055
MPV[2]	0,118	0,933	0,159
Neu/lymp[3]	0,132	0,349	0,054

1: C reactive protein 2: Mean platelet volume
3: Neutrophil/ Lymphocyte
(One way Anova test)

Among the children with viral lower respiratory tract infection, a positive statistically significant correlation between MPV level and lymphocyte level was observed whereas there was a negative statistically significant correlation between MPV level and CRP, Platelet, Neu, and Neu / lymp levels ($p < 0.05$). MPV level of the children with bacterial lower respiratory tract infection was found to have a positive statistically significant correlation and a negative statistically significant correlation with lymphocyte level and neutrophil level, respectively ($p < 0.05$) (Table 5).

Table 5. Correlations between MPV value of groups and other variables

		MPV[2]	
		rho	**p**
Viral Lower Respiratory Tract Infection	**CRP[1]**	-0,170	**0,003**
	Leukocyte	-0,085	0,147
	Hematocrit	0,058	0,320
	Platelet	-0,166	**0,004**
	Neutrophil	-0,245	**<0,001**
	Lymphocyte	0,242	**<0,001**
	Neu/lymp[3]	-0,245	<0,001
Bacterial Lower Respiratory Tract Infection	**CRP[1]**	-0,042	0,790
	Leukocyte	-0,201	0,197
	Hematocrit	-0,108	0,492
	Platelet	-0,186	0,232
	Neutrophil	-0,299	**0,049**
	Lymphocyte	0,303	**0,047**
	Neu/lymp[3]	-0,294	0,056

1: C reactive protein 2: Mean platelet volume
3: Neutrophil/ Lymphocyte (Spearman Correlation Analysis)

Considering the whole patient group in terms of laboratory values, the highest value of the platelet count was 917,000 / mm3, and platelet count of 117 (34 %) patients exceeded 400,000. 35 of them (81% of the bacterial pneumonia) were bacterial while 82 of them (27 % of viral pneumonia) were viral pneumonia. The lowest platelet value was 93,000 mm3 among all patients. Platelet values of 8 (3.3 %) patients were found to be lower than150,000. Of them,6 and 2 had viral and bacterial pneumonia, respectively.

DISCUSSION

There was no statistically significant difference in age and gender between the patient groups with viral and bacterial pneumonia ($p > 0.05$). In the studies about LRTI in childhood, the dominance of male gender was determined to be as high as 1.25: 1 and 2: 1.5 Although we found a higher value (M / F = 1.32) in our study, we found no statistically significant difference ($p = 0.410$) (Table 1).

The World Health Organization determined cough and tachypnea as the main findings for pneumonia. It points out to a quite sensitive situation and bacterial pneumonia with a low specificity.[11] The patients in the group were primarily diagnosed based on the clinical findings. The discrimination between bacterial and viral pneumonia is still a challenging issue despite all of the clinical and laboratory procedures.[12]

In a review, it was reported that chest radiography was not very effective in making a discrimination between viral and bacterial pneumonia.[13] The studies which use lung aspirates showed the presence of bacterial cause at a rate between 28 % and 82 % in lobar or bronchopneumonia.[14] In a prospective study which investigated multiple pneumonia agents, it was stated that even interstitial pneumonia was led by viral (50 %) and bacterial (50 %) causes.[15] Apart from small atelectasis, segmental or focal consolidations and alveolar infiltrations suggest bacterial pneumonia rather than bronchiolitis. Nevertheless, only radiological findings may be insufficient to determine the etiology. Therefore, evaluation of the diagnosis with clinical and other laboratory findings is recommended.[16]

In general, the infants with bacterial pneumonia can have higher fever and a worse general condition and their laboratory findings may occasionally indicate a serious bacterial infection. Focal crepitation in the lung and focal infiltrates on chest radiography may be helpful in the differential diagnosis, but a complete discrimination may not be made with clinical findings. It is emphasized that it will

be rational to make a treatment plan just like in bacterial pneumonia in such cases.[17] In another literature, it is recommended in cases of suspected pneumonia that chest radiography is taken and treatment planning is made based on the clinical findings.[18] Lobar and dense segmental infiltrations were evaluated in favor of bacterial pneumonia while segmental and peribronchial infiltrations with less intensity were classified in viral pneumonia.

In our study, there was a significant difference only in CRP between the groups with viral and bacterial radiographic findings (P=0,015, Table 3). In a study in literature, 77% of sensitivity was detected according to 37.1 mg / L cut-off value of CRP in discriminating between bacterial pneumonia and RSV pneumonia.[17] Several studies indicate that CRP is a diagnostic determinant for community-acquired pneumonia (CAP).[19,20] It is stated that CRP is a useful examination for discriminating especially between pneumonia and asthma attack and is a guide for the necessity of antibiotic treatment.[21] In a study, CRP value was found significantly higher in the bacterial/mixed aetiology group than in the viral aetiology pneumonia group in children.[22] In other study, CRP was found significantly higher in children with pneumonia caused viral-bacterial co-infections($p = 0.007$).[23] CRP, interleukin-6,8, and procalcitonin levels, have the potential to predict severe CAP in pediatric populations.[24] Biomarkers of inflammation, such as white blood cell counts (WBCs), procalcitonin (PCT), and CRP, have been described in children as useful markers associated with severe pneumonia.[25] Such biomarkers may be useful in the management of patients with CAP.[25,26] CRP, an acute-phase protein that is triggered in response to nonspecific inflammation and/or tissue damage.[27,28] Production of CRP occurs mostly in the liver and is induced by IL-6 and TNFα.[27,28]

CRP has great clinical utility, as shown by the meta-analysis results reported here. In pediatric CAP, many studies have shown that elevated CRP levels are associated with unfavorable outcomes, such as lobar consolidation, fever, long hospital length of stay, pleural effusion, and even death.[27]

In a contrary review, it was specified that CRP did not change the decision to write and use antibiotics in CAP in the outpatient clinic.[29] While there is unclear contradictory information about CRP, we found out in this study on children that the high level of CRP supports such diagnosis in pediatric patients with radiological findings which suggest bacterial pneumonia even if we could not find the cut-off value. In pneumonia guide of the National Institute for Health and Care Excellence (NICE) published in 2014, it was reported that CRP is a useful test for the diagnosis of pneumonia.

Platelet distribution width(PDW) act as an acute phase reactant in inflammatory diseases.[9]

Thrombocytosis is a very frequently-seen finding during the course of pediatric infections. It was shown that platelets respond during infections, similar to leukocytes.[30] Both of them are activated with a microbial event. While leukocytes phagocytize bacteria, platelets get microorganisms into phagosome-like vacuoles. Thus, the clearance of pathogens is accelerated.[31] It is reported that thrombocytosis is usually seen in infections of enclosed areas such as bone, joint and pleural cavity.[32] Although it is accepted that it is more likely to occur in bacterial infections that have more severe clinical picture, high platelet counts were detected in bronchiolitis and pneumonia group with viral etiology in recent years.[33] In our cases, thrombocytosis was observed in 81% of bacterial pneumonia and in 27% of viral pneumonia. Most of these patients were in the viral lower respiratory tract infection group. This is consistent with the presence of thrombocytosis rather than thrombocytopenia in cases of bacterial and pulmonary parenchymal and pleural involvement. In the bacterial group, we found that the means of platelet and MPV were higher than those of the viral pneumonia group. However, we could not find statistical significance (P>0,05).

In a study of Prina et al. that examined 2423 inpatients with community-acquired pneumonia, 2% of the patients had thrombocytopenia, 8 % of them had thrombocytosis while 90% of them had normal platelet count.[34] Mirsaeidi et al. was asserted that thrombocytopenia and thrombocytosis were significantly associated with mortality in community-acquired pneumonia.[31] In other studies which included in pediatric patients, similar relationships between thrombocytosis and poor clinical outcome in patients with pneumonia were reported.[15,19]

An increase in MPV is associated with an increased growth of megakaryocytes in response to thrombopoietic stress. [9,31]. Two mechanisms were proposed for the role of platelets in patients with pneumonia. One of them is the effects for stimulating the systemic inflammation. They induce secretion of various proinflammatory cytokines by stimulating chemotaxis.[35] It is believed that interleukin-6 (IL-6) which plays an important role in the inflammatory process of community-acquired pneumonia affects MPV. It was indicated that cytokines such as IL-3 and IL-6 induce the formation of larger and more reactive platelets by triggering megakaryocytes.[36] The thrombus formation induced by was shown as the second mechanism and it was stated that this mechanism leads tothe relationship between having pneumonia and myocardial infarction in adults.[35]

Karadağ et al., lower MPV levels were observed in patients with pneumonia compared to the healthy control group.[9] Robbins et al. reported that the changes in platelet size show at least two patterns: early increase in MPV in severe infections such as septicemia, and late decrease in MPV in chronic bacterial infections.[36] Even though there was no statistical significance in our bacterial pneumonia group, a lower MPV was observed.In groups of viral and bacterial pneumonia, there was a significant correlation with MPV lymphocyte while it was negatively correlated with neutrophils. Thrombocytosis existed in 81% and 21% of the bacterial viral pneumonia, respectively. Of 8 patients with thrombocytopenia, 6 were in the viral group and 2 were in the bacterial group. Platelet increase with CRP acts as an acute phase in bacterial pneumonia. In both of the viral and bacterial groups, MPV has a significant correlation with lymphocyte which is directly proportional, and is correlated with neutrophils which is inversely proportional as well, so MPV is higher in viral infections whereas it is lower in bacterial infections.

Increased MPV indicates the activation of platelet.[37] Nevertheless, it was reported that in case of inflammation, the only difference is seen in the internal structure of the platelet membrane and that microtubular depolymerization structure change in response to inflammation and alter the shape of the platelet.[38,39] The greatest shortfall of our retrospective study was that the changes in laboratory parameters were not followed at different time intervals during the course of the disease.

In conclusion, even if we could not obtain a significant cut-off value in community-acquired lower respiratory tract infections,we can primarily consider the bacterial pneumonia and make a decision on the empirical antibiotic more easily when CRP value is high in parallel with the radiological findings.

This study was performed following approval from the Haseki Hospital ethical committee (The chair person: Dr Fuat Şar, No 584, Approval date: 21.11.2017).

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No any support

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