Neutrophil/lymphocyte and C-reactive protein/mean platelet volume ratios in differentiating between viral and bacterial pneumonias and diagnosing early complications in children

Mervan Bekdas, MD, Sevil B. Goksugur, MD, Esma G. Sarac, MD, Mustafa Erkocoglu, MD, Fatih Demircioglu, MD.

ABSTRACT

الأهداف: لاختبار قابلية استخدام معدلات الخلايا المتفاعلة / اللمفاوية (N/L) وبروتين الارتكاسي C / حجم الصفائح الدموية (MPV/CRP) للتشخيص التفريقي لبكتيريا الالتهاب الرئوي الفيروسي، ضد التشخيص المكبر لمضاعفات تتعلق بالالتهاب الرئوي.

الطريقة: أجريت هذه الدراسة بأثر رجعي على 31 مريضاً اللذين شخصوا بالالتهاب الرئوي الجرثومي و 21 مريضاً شخصوا بالالتهاب الرئوي الفيروسي خلال الفترة من يناير 2011م إلى ديسمبر 2012م في قسم طب الأطفال، كلية الطب، جامعة ابانت عزت بايسل، بولو، تركيا. و قد تحققنا من الخصائص الإكلينيكية والإشعاعية والنتائج المخبرية للمرضى من خلال سجلاتهم الطبية.

النتائج: نسبة الإناث / الذكور من المرضى اللذين يعانون من البكتيريا كانت1.8 /1.0. والالتهاب الرئوي الفيروسي كان 1.0/2.0. كان متوسط عمر المريض 59±51 شهراً. كان هناك فروق إحصائية في الخلايا المتفاعلة/ نسبة الخلايا اللمفاوية (2.7 versus .06، p<0.001) ونسبة CRP / MPV (11.0 versus 9.3، p<0.001) في حالات الالتهاب الرئوي الجرثومي مقابل أولئك اللذين لديهم فيروس الالتهاب الرئوي. و9 من المرضى حددوا بوجود مضاعفات. كان هناك اختلافاً إحصائياً واضحاً في N/L (3.5 versus 1.2، p=0.01) نسبة CRP/MPV (11.1 versus 3.9، p=0.001) في الحالات التي تطورت فيها المضاعفات مقارنة مع تلك التي لم تتطور. عندما استخدمت معدلات الخلايا المتفاعلة / اللمفاوية و CRP/MPV معاً، يمكن تقدير تشخيص الالتهاب الرئوي الجرثومي بشكل صحيح في 28 حالة (90.3%) (odds ratio [OR]=0.06،95% confidence interval [CI]:0.01–0.29، p<0.001) وكان متوقع مضاعفات الالتهاب الرئوي في 8 حالة (88.9%) (OR=13.5،95% CI:1.5 –118.1،p=0.005).

الخاتمة: لوحظ الجمع بين استخدام نسبة N/L و MPV/CRP في تشخيص التفريقي للبكتيريا مقابل الالتهاب الرئوي و التنبؤ بالمضاعفات.

Objectives: To test the usability of neutrophil/lymphocyte (N/L) and C-reactive protein/mean platelet volume (CRP/MPV) ratios for the differential diagnosis of bacterial versus viral pneumonia, and the early diagnosis of complications related to pneumonia.

Methods: This retrospective study was conducted on 31 patients diagnosed with bacterial pneumonia and 21 patients diagnosed with viral pneumonia from January 2011 to December 2012 in the Department of Pediatrics, Faculty of Medicine, Abant Izzet Baysal University, Bolu, Turkey. We investigated the clinical characteristics, radiological, and laboratory findings of patients from their medical records.

Results: The female/male ratio of patients with bacterial was 1.0/1.8, and with viral pneumonias was 1.0/2.0. The mean patient age was 59±51 months. There was a statistically significant difference in the neutrophil/lymphocyte ratio (2.7 versus 0.6, $p<0.001$) and CRP/MPV ratio (11.0 versus 9.3, $p<0.001$) in the cases with bacterial pneumonia versus those who had viral pneumonia. Nine of the patients were identified as having complications. There was a statistically significant difference in the N/L ratio (3.5 versus 1.2, $p=0.01$) and CRP/MPV ratio (11.1 versus 3.9, $p=0.001$) in the cases that developed complications compared with those that did not. When the neutrophil/lymphocyte and CRP/MPV ratios were used jointly, the diagnosis of bacterial pneumonia could be correctly estimated in 28 (90.3%) cases (odds ratio [OR]=0.06, 95% confidence interval [CI]: 0.01-0.29, $p<0.001$) and pneumonia-related complications were predicted in 8 (88.9%) cases (OR=13.5, 95% CI: 1.5-118.1, $p=0.005$).

Conclusions: It was observed that the combined use of N/L and CRP/MPV ratios might be used in both the differential diagnosis of bacterial versus viral pneumonia, and the prediction of complications.

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From the Department of Pediatrics, Faculty of Medicine, Abant Izzet Baysal University, Bolu, Turkey.

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Address correspondence and reprint request to: Dr. Mervan Bekdas, Assistant Professor, Department of Pediatrics, Faculty of Medicine, Abant Izzet Baysal University, Golkoy 14290, Bolu, Turkey. Tel. +90 (374) 2534656. E-mail: merbek14@yahoo.com

Pneumonia often presents with inflammation that occurs in the pulmonary parenchyma in response to infectious agents. The diagnosis for patients presenting with fever and respiratory symptoms is made on the basis of physical examination, or chest radiography findings, or both.[1,2] Pneumonia is an important reason for morbidity and mortality among children below the age of 5 throughout the world.[3] Every year, nearly 200 million cases of pneumonia are identified among children below the age of 5.[4] Pneumonia causes the death of nearly 2 million of these children. Globally, pneumonia accounts for one fifth of pediatric deaths.[5,6] The non-specific period occurring in the host in response to infection, inflammation, and trauma is known as the acute phase. The damage occurring as a result of these causes activates neutrophils and macrophages, which are local inflammatory cells and the liver generates acute phase proteins in response to the cytokines (tumor necrosis factor [TNF], interleukin [IL]-1, and IL-6) secreted by these cells.[7] In daily practice, acute phase responses are widely used in distinguishing between bacterial and viral infections. The acute phase responses that are most often used in clinical practice are the leukocyte count (WBC), absolute neutrophil count, erythrocyte sedimentation rate (ESR), and serum C-reactive protein (CRP) level.[8] There are various publications on the use of the neutrophil (N)/lymphocyte (L) ratio to assess various clinical conditions. This ratio was especially useful in the diagnosis of acute appendicitis,[9] and acute pancreatitis.[10] Also, the mean platelet volume (MPV), which is one of the hemogram parameters, is also affected by many inflammatory conditions.[11,12] For pneumonia, treatment success is increased as a function of the time treatment is started, which is only possible via early diagnosis. This study is aimed at testing the combined usability of N/L and CRP/MPV ratios as laboratory parameters, which may provide additional benefits in both the differential diagnosis of bacterial versus viral pneumonia, and in the early recognition of complications that may develop as a result of these clinical pictures.

Methods. This study retrospectively examined the records of 85 cases diagnosed as having pneumonia in the pediatric clinics of our hospital between January 2011 and December 2012 in the Department of Pediatrics, Faculty of Medicine, Abant Izzet Baysal University, Bolu, Turkey. Approval from the local Ethics Committee was obtained prior to commencing, and the study was carried out according to principles of the Helsinki Declaration.

The clinical picture accompanied by the findings of fever, tachypnea, intercostal retractions, and rales was accepted as pneumonia[13] and included in the study. Respiratory counts over 55/min for children under the age of 3 months, 40/min between 3-11 months, 25-30/min between 1-5 years, and 22/min above the age of 5 years were considered as tachypnea.[14] The patients who had nasal discharge, intercostal retraction, wheezing in their physical examination, and interstitial infiltrations in their pulmonary x-rays were considered to have viral pneumonia.[15] The cases identified to have an effusion or pulmonary abscess during treatment were accepted as complicated pneumonia cases. The results of blood, pleural effusion, sputum, and abscess material culture tests were recorded. The age, gender, season of presentation, symptoms during presentation (fever, cough, nasal discharge, nasal flaring, and wheezing), physical examination findings (tachypnea, inter-costal retraction, and rales and rhonchi), laboratory findings (hypoxemia, whole blood count [platelet (PLT), MPV, WBC, N, L], CRP, ESR), and chest radiography findings were recorded. The blood tests were performed on admission to the hospital. None of the patients had received steroid therapy. Child and adolescent age groups were included in the study except for newborns and those with missing file information; 33 cases, which had congenital heart disease, tuberculosis, malnutrition, and diagnosed with recurrent pneumonia were excluded from the study.

The data were evaluated using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 15.0 for Windows. For statistical evaluation, the Student's-t and Mann-Whitney U tests were used depending on the data type. The Receiver operating characteristic (ROC) curve analysis was used for the regression analysis and cut-off values. A p-value <0.05 was considered significant.

Results. A total of 52 patients were enrolled in the study. Thirty-four (65.3%) of the patients were male and 18 (34.6%) of them were female. Their average age was 59±51 months ranging from one to 144 months. Twenty one (40.3%) of the patients presented in winter, 13 (25%) in spring, 14 (26.9%) in summer, and 7 (13.4%) in autumn. Only 8 children were able

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Table 1 - Comparison of the characteristics of cases with bacterial and viral pneumonia included in a study conducted in the Department of Pediatrics, Faculty of Medicine, Abant Izzet Baysal University, Bolu, Turkey (N=52).

Characteristics	Bacterial pneumonia (n=31)	Viral pneumonia (n=21)	*P*-value
Age (months), median (min-max)	72 (24-144)	18 (2-84)	0.009*
Gender (M/F), n (%)	20/11 (64.5/35.4)	14/7 (66.6/33.3)	0.87*
Admission season[2] (Winter/Summer), n (%)	12/8 (38.7/25.8)	9/6 (42.8/28.5)	0.78*
PLT (/l), mean±SD	402387±138760	387190±174587	0.58†
MPV (fl), mean±SD	7.9±1.3	8.2±1.5	0.45†
WBC (/l), median (min-max)	12020 (7800-15600)	8280 (5700-12900)	0.001*
N (/l), median (min-max)	7900 (4000-11600)	3020 (1000-5100)	<0.001*
L (/l), median (min-max)	3100 (1430-6700)	4525 (2700-6100)	0.33*
N/L, median (min-max)	2.7 (1.1-5.3)	0.6 (0.2-1.3)	<0.001*
CRP/MPV, median (min-max)	11.0 (3-26.9)	9.3 (0.1-4.9)	<0.001*
CRP (mg/dl) median (min-max)	78.7 (22.8-160)	3.4 (0.2-29)	<0.001*
ESR (mm/h) median (min-max)	50.0 (11-102)	14.0 (6-54)	0.02*
Complication, n (%)	8 (25.8)	1 (4.7)	0.051*

PLT - platelet, MPV - mean platelet volume, WBC - leukocyte count, n - neutrophil, L - lymphocyte, CRP - C-reactive protein, *Mann-Whitney U test, †Student-t test

Table 2 - Comparison of the characteristics of pneumonic cases with and without complications included in a study conducted in the Department of Pediatrics, Faculty of Medicine, Abant Izzet Baysal University, Bolu, Turkey (N=52).

Characteristics	Pneumonia without complications (n=43)	Pneumonia with complications (n=9)	*P*-value
Age (months), median (min-max)	33 (2-144)	112 (60-144)	0.14*
Gender (M/F), n (%)	30/13 (69.7/30.2)	6/3 (66.6/33.3)	0.93*
Admission season (Winter/Summer), n (%)	18/8 (41.8/18.6)	3/3 (33.3/33.3)	0.8*
PLT (/l), mean±SD	404222±137464	390186±157506	0.79†
MPV (fl), mean±SD	7.6±0.9	8.1±1.5	0.38†
WBC (/l), median (min-max)	9380 (5700-15600)	12020 (10000-15000)	0.27*
N (/l), median (min-max)	4815 (1000-9810)	8800 (4940-11600)	0.068*
L (/l), median (min-max)	3600 (1430-6700)	2900 (2190-3930)	0.07*
N/L, median (min-max)	1.2 (0.2-5.3)	3.5 (1.2-5)	0.01*
CRP/MPV, median (min-max)	3.9 (0.1-14.5)	11.1 (3.3-26.9)	0.001*
CRP (mg/dl) median (min-max)	25.9 (0.2-94.7)	81.7 (25.7-160)	0.002*
ESR (mm/h) median (min-max)	20.5 (6-93)	63.0 (33-102)	0.064*

PLT - platelet, MPV - mean platelet volume, WBC - leukocyte count, n - neutrophil, L - lymphocyte, CRP - C-reactive protein, *Mann-Whitney U test, †Student-t test

to give sputum samples, and the culture results were all negative. We identified only one of the 10 (10%) patients whose blood culture we checked as having a positive culture. The characteristics of bacterial and viral pneumonia cases are provided in **Table 1**. According to the statistical assessment based on the comparison of the 2 groups, the ages of patients, WBC values, neutrophil values, neutrophil/lymphocyte ratio, CRP/MPV ratio, CRP values, and ESR values were identified to be significantly, different whereas no

Table 3 - The cut-off values of bacterial pneumonic cases.

Characteristics	Cut-off	Sensitivity %	Specificity %	Area	CI 95%	*P*-value
N/L	1.7	74.2	76.2	86.9	77-96	<0.001
CRP/MPV	2.6	80.6	81.0	88.9	80-97	<0.001

MPV - mean platelet volume, N - neutrophil, L - lymphocyte, CRP - C-reactive protein, CI - confidence interval

Table 4 - Cut-off values of pneumonic cases that developed complications.

Characteristics	Cut-off	Sensitivity %	Specificity %	Area	CI 95%	*P*-value
N/L	2.7	77.8	79.1	77.5	62-92	0.01
CRP/MPV	7.8	77.0	79.0	85.0	70-99	0.001

MPV - mean platelet volume, N - neutrophil, L - lymphocyte, CRP - C-reactive protein, CI - confidence interval

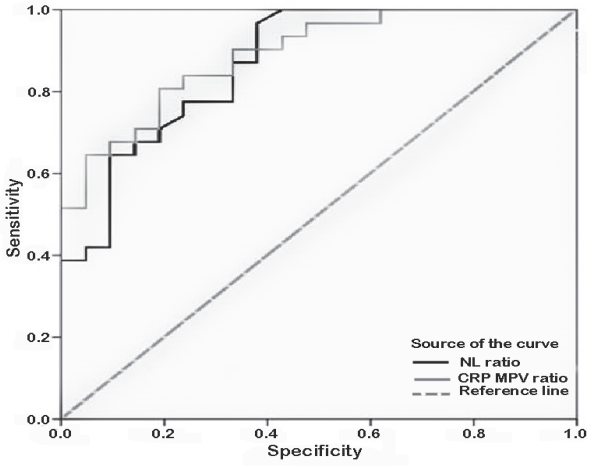

Figure 1 - Cut-off values for bacterial pneumonia diagnosis based on neutrophil (N)/lymphocyte (L) and C-reactive protein (CRP)/mean platelet volume (MPV) ratios.

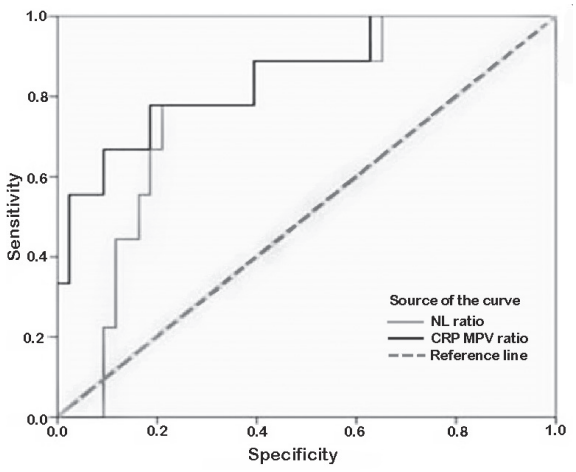

Figure 2 - Cut-off values for the possibilities of the development of pneumonia complications as neutrophil (N)/lymphocyte (L) and C-reactive protein (CRP)/mean platelet volume (MPV) ratios.

significant differences were identified in the statistical assessment made for the other variables. Nine (17.3%) of our patients were identified to have complications. Eight (15.3%) of these cases were diagnosed with bacterial pneumonia and one (1.9%) of them with viral pneumonia. Three (5.7%) of the patients presented in winter, one (1.9%) in spring, 3 (5.7%) in summer, and 2 (3.8%) in autumn. Pleural effusion or abscess material cultures were negative. The characteristics of patients who developed and did not develop complications are provided in **Table 2**. According to the statistical assessment based on the comparison between the 2 groups, the neutrophil/lymphocyte ratios, CRP/MPV ratios, and CRP values were found to be significantly different, and no significant differences were identified for the other variables based on the statistical assessment made ($p>0.05$). The cut-off values for the bacterial pneumonia diagnosis based on N/L and CRP/MPV ratios are provided in **Table 3** and **Figure 1**. The N/L cut-off value for bacterial pneumonia diagnosis was found to be 1.7, and the CRP/MPV cut-off value was found to be 2.6. The cut-off values for the possibilities of the development of pneumonia complications as per N/L and CRP/MPV ratios are provided in **Table 4** and **Figure 2**. The N/L cut-off value for the development of pneumonia complications was found to be 2.7, and the CRP/MPV cut-off value was found to be 7.8.

Discussion. Our study showed that the N/L ratios and CRP/MPV ratios of children with bacterial pneumonia were significantly higher than those in patients with viral pneumonia, and that these values were associated with the development of complications.

The agents of pneumonia in children below 5 years of age are viral,[16] on the other hand, they are frequently bacterial in children above 5 years of age.[17] Our results are consistent with the literature. The 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.[18] The ESR is used to assess the progression of a disease as well as treatment response. In most of the bacterial infections, ESR is elevated whereas it is generally normal or slightly high

for viral infections.[19] In our study, we identified that CRP and ESR were high at a significant level among the bacterial pneumonia cases. The literature also contains publications indicating that these parameters may not be used for differential diagnosis.[20]

The higher the severity of the pneumonia, the higher is the probability that complications will occur. One of the most important complications is pleural effusion, and it can be identified in 15.6-50% of the cases.[21,22] It is very important to recognize these complications, which increase hospital stay and costs, at an early stage. There are studies in the literature associating CRP with the development of effusion,[23] whereas there are also studies indicating that ESR is more important than CRP.[24] The CRP level was significantly higher in patients with complications related to pneumonia than in patients who did not have complications.

Leukocytosis and neutrophilia may occur with infectious diseases. However, these parameters are not enough to distinguish between bacterial and viral infections.[25] The use of the N/L ratio in the differential diagnosis of viral and bacterial pneumonia is rare.[26] In our study, we identified that the increased N/L ratio in bacterial pneumonia is an important parameter, which may help in its discernment from viral pneumonia. With the N/L cut-off value for bacterial pneumonia diagnosis taken as 1.7, more significant results can be obtained (p<0.001). The cut-off value that could be accepted for the same parameter in relation to the possibility of complication development with pneumonia was 2.7 (p=0.01). Another parameter we identified in our study was the CRP/MPV ratio. This parameter showed a significant difference for both the bacterial-viral pneumonia differentiation (for cut-off value 2.6, p<0.001), and the identification of whether complications would develop or not (for the cut-off value 7.8, p=0.001).

In our study, the bacterial pneumonia diagnosis was correctly made for 28 cases (90.3%) when the N/L and CRP/MPV ratios could be used jointly (odds ratio [OR]=0.06, 95% confidence interval [CI]: 0.01-0.29, p<0.001). When the 2 variables were again used jointly, 8 cases (88.9%) could be correctly diagnosed with complications arising from pneumonia (OR=13.5, 95% CI: 1.5-118.1, p=0.005).

One of the most important limitations of our study was that the number of patients was low; the other was that we were not able to isolate agents in the pleural effusion or pulmonary abscess materials. Normally, the possibility of being able to generate agents from pleural effusion is approximately 45%.[27] Since our hospital is a tertiary health-care facility, our patients were referred to our hospital mostly after their initial treatment was started at other facilities. This situation might have eliminated our chance of being able to generate agents in the cultures. The chance of being able to generate agents in the blood cultures of pneumonic patients ranges between 8.8-16% among hospitalized patients.[28,29] We identified in our study that there was growth in 10% of the blood cultures, which was in line with the literature. We did not evaluate the presence of mycoplasma serologically. Additionally, we could not evaluate viral agents in our patients due to the cost-effectiveness of these tests.

In conclusion, the combined use of N/L and CRP/MPV seems feasible in differentiating between bacterial and viral pneumonia (cut-off values of 1.7 and 2.7) as well as prediction of complications, which may develop as a result of pneumonia (cut-off values of 2.6 and 7.8) but more comprehensive studies are required to help establish the role of these parameters in differentiating between viral and bacterial pneumonia.

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