J Nepal Health Res Counc 2016 Sep- Dec;14(34):154-8

C-reactive Protein Versus Neutrophil/lymphocyte Ratio in Differentiating Bacterial and Non-bacterial Pneumonia in Children

Eva Gauchan,[1] Sudhir Adhikari[1]

[1]Department of Pediatrics, Manipal Teaching Hospital, Pokhara, Nepal.

ABSTRACT

Background: Pneumonia is a leading cause of childhood mortality in a low resource country. Simple laboratory markers can help differentiate between bacterial and non-bacterial pneumonias for appropriate management.

Methods: In children aged one to 60 months with features of lower respiratory infection, C-reactive protein (CRP) and neutrophil-lymphocyte ratio (NLR) were used to differentiate between bacterial and non-bacterial pneumonias. The cutoff values for detecting bacterial pneumonias were evaluated by statistical tools.

Results: Bacterial pneumonia was diagnosed in 285 (43.6%) children out of 654 studied. At a cut-off value of 36 mg/L CRP was predictive of bacterial pneumonias with sensitivity and specificity of 61.8% and 91.3% respectively while the sensitivity and specificity for predicting bacterial pneumonia using NLR was 45.6% and 64% respectively with 1.28 used as a cut-off.

Conclusions: Our study shows that CRP is superior to NLR in differentiating bacterial from non-bacterial pneumonias in children.

Keywords: Bacterial and non-bacterial pneumonia; C-reactive protein; neutrophil to lymphocyte ratio.

INTRODUCTION

An estimated 6.3 million children <5 years of age died world-wide in 2013 with South Asia contributing to a third (32.1%; 2.015 million) of the deaths.[1] Pneumonia was, by far the commonest cause of death with 0.935 million (14.9%) children dying during that period.[1] However, there has been a reduction in the pneumonia-related deaths by 24.3% in 2013 as compared to 2000.[1] In Nepal, over the past 15 years there has been a surge in the number of cases seeking treatment for pneumonia in a health care facility from 18% in 1996 to 50% in 2011[2] and pneumonia was found to be a leading cause of morbidity and mortality (NDHS 2011).[2] Early diagnosis and treatment with antibiotics play a major role in reducing the number of deaths.

Various laboratory markers are used in differentiating the etiology of pneumonias,for example, white cell count, absolute neutrophil count, neutrophil to lymphocyte ratio (NLR), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum procalcitonin, etc.[3-10] Procalcitonin is better in diagnosing bacterial infections,[3-4] but this test is not done routinely in our laboratory. Hence, we have chosen CRP and NLR which are less expensive, quick and easy to perform.

METHODS

This study was conducted in a tertiary level hospital in Western Nepal during May 2013 till April 2016. All children aged between one to 60 months with fever, cough, fast breathing with chest retractions and auscultatory evidence of lower chest findings were included. Pneumonia was classified as bacterial in presence of fever above 101° F, crepitations and any of the following radiologic features: alveolar infiltrates, lobar consolidation, pleural effusion with or without positive cultures.Those with interstitial infiltrates, hyperinflation or normal chest X-ray with clinical evidence of conjunctivitis or rhinorrhea with or without low-grade fever, predominant wheezing and negative cultures were classified as non-bacterial pneumonia.

Complete blood count was analyzed by H3D Premier Automated Hematology Analyzer and NLR was calculated from the percentage of circulating neutrophil

Correspondence: Dr Eva Gauchan, Department of Pediatrics, Manipal Teaching Hospital, Pokhara, E-mail: evagauchan@gmail.com, Phone: +977 9856034568.

and lymphocyte. The CRP was analyzed by slide latex agglutination test; values equal to or >6 mg/L was taken as positive. Blood culture was done in all cases while pleural fluid cultures were done when there were features of a pleural effusion and chest X-ray was done in all patients. Chest x-ray was read by the pediatrician on duty and findings confirmed by the consultant radiologist.

Neonates, children having major congenital anomalies which disrupted normal functioning and two or more admissions for pneumonias were excluded from the study. Data was analyzed with SPSS version 19 and reported as mean ± SD. The cut-off values as well as the diagnostic accuracy of CRP and NLR for determining bacterial pneumonia was evaluated by receiver operating curves (ROC) analysis and the area under the curve (AUC) was calculated. The sensitivity and specificity with their 95% confidence intervals were reported. A p value of <0.05 was taken as significant.

RESULTS

There were 939 children with a diagnosis of pneumonia during the study period. Among them, 285 children were excluded due to incomplete records. Data on 654 children were analyzed. There were 428 (65.4%) males and 226 (34.6%) females (ratio 1.9:1). Bacterial pneumonia was diagnosed in 285 (43.6%) and non-bacterial in 369 (56.4%). The mean age was 11.2±11.5 months. Non-bacterial pneumonia was seen in children at lower age than bacterial pneumonia (p=0.007).

The mean values of WBC count (p=0.0020) and ANC (p=0.001) were significantly higher in the group with bacterial pneumonia than in non-bacterial pneumonia. The NLR did not show any significant difference between the two groups. The mean value of CRP was higher in the bacterial pneumonia (45 ±33.6mg/L) than non-bacterial (10±16.3mg/L). This finding was statistically significant (p=<.001).

The ROC analysis of CRP and NLR was done to differentiate children with bacterial pneumonia with CRP showing better sensitivity and specificity as compared to NLR (Fig.1).

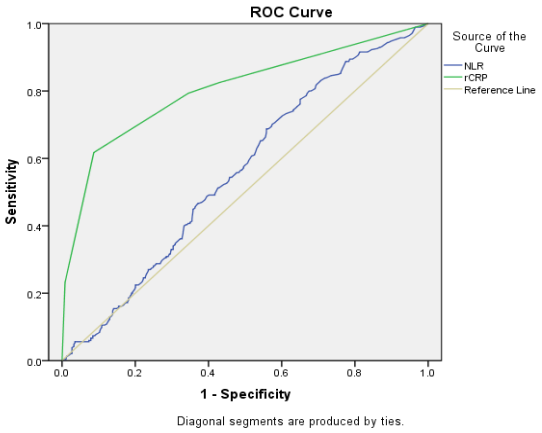

Fig.1. ROC curve of CRP and NLR in diagnosing bacterial pneumonia in children aged one to 60 months.

A cut-off value of ≥36 mg/L for CRP was associated with a sensitivity of 61.8% and specificity of 91.3% (p=<0.001)

Table 1. Bacterial and non-bacterial pneumonia in children of one to 60 months of age.

Characteristics	Bacterial Pneumonia (n= 285)	Non-bacterial Pneumonia (n=369)	p-value
Age (months), mean (± SD)	12.7 (±12.8)	10 (±10.3)	0.007*
Sex (M/F), n (%)	180/105 (63/37)	248/121 (67/33)	0.28
WBC count /cu.mm, mean (± SD)	14422 (±10312)	12354 (±5012)	0.002*
ANC/cu.mm, mean (± SD)	7836 (±7303)	6130 (±4525)	0.001*
ALC/ cu.mm, mean (± SD)	6295 (±5204)	6008 (±3302)	0.416
NLR, mean (± SD)	1.8 (±2.08)	1.67 (±2.25)	0.468
CRP (mg/L), mean (± SD)	45 (±33.6)	10 (±16.3)	0.000*

Note: SD- standard deviation; M/F-male/female ratio; WBC(white blood cell count); ANC- absolute neutrophil count; ALC- absolute lymphocyte count; NLR- neutrophil/lymphocyte ratio; CRP- C-reactive protein

Table 2. Cut-off values of CRP and NLR in cases with bacterial pneumonia in children aged one to 60 months.

Characteristics	Cut-off value	Sensitivity %	Specificity %	AUC	95% CI	p-value
CRP (mg/L)	36	61.8	91.3	80.5	77-84	<.001
NLR	1.28	45.6	64	56.0	51.6-60.4	0.009

in detecting bacterial pneumonia. As for NLR, a cut-off value of ≥1.28 showed sensitivity of 45.6% and specificity of 64% in bacterial pneumonia. The AUC for CRP and NLR were 80.5 and 56 respectively (Table 2).

Blood culture was positive in 36 cases (12.6%) of bacterial pneumonia. Staphylococcus aureus was the most common organism isolated (n=11) followed by Pseudomonas (n=5), Enterobacter (n=4), Coagulase negative Staphylococcus aureus (CONS) (n=3) and Klebsiella pneumonia (n=3). In one case, pleural fluid culture isolated Staphylococcus aureus with blood culture showing no growth.

DISCUSSION

Our study shows that CRP values were significantly higher in the bacterial group compared to non-bacterial pneumonia group (45 ±33.6 mg/L vs 10±16.3 mg/L). When we took a cut-off value of 18mg/L for detecting bacterial pneumonias, the sensitivity was 73% and specificity was 74%. However when a cutoff of 36 mg/L was taken, the sensitivity decreased to 61.8% and specificity increased to 91.3%. The area under the ROC curve (AUC) was 80.5 (95% CI: 77-84) (p=<0.001). This finding is similar to that found by several authors.[5-9]

CRP is an acute phase protein secreted by the liver within six hours of onset of inflammation. It rises rapidly in infections and is cleared as rapidly with recovery. CRP level has been found to be higher in bacterial than in non-bacterial infections in various studies and it was found to be a useful marker for differentiating bacterial etiology of infections.[3,5,6,8-9,11] A CRP value above 20 mg/L has been suggested as a demarcation to differentiate between bacterial from viral infections.[12]

A normal physiological response to infections is seen as an increase in neutrophils and decrease in lymphocyte count. The NLR has been found to be useful in diagnosis of bacterial infections in several studies especially in acute appendicitis.[10,13-16] In contrast to CRP, we could not find statistically significant difference in the NLR between the two groups(p=0.468). A study conducted by Bekdas et al showed the diagnostic performance of NLR when used to differentiate bacterial from viral pneumonias; significant results were obtained when a NLR cut-off of 1.7 was taken.[7] Similarly, other studies have shown that NLR can be used to distinguish bacterial from other pneumonias.[7,15] In our study when a NLR cut-off of 1.28 was taken, the sensitivity and specificity were 45.6% and 64% respectively with AUC 56 (95% CI: 51.6-60.4).

The total leucocyte counts as well as the absolute neutrophil count were higher in the bacterial group compared to the non-bacterial group. Both these findings were statistically significant (p=0.002 and p=0.001 respectively). This finding is similar to some studies[7,9,17,18] unlike the findings by Virkki et al with no difference in the leucocyte count between the two groups.[6]

The organisms causing pneumonia vary with age. Viral pneumonias tend to occur at a younger age and viruses are frequently identified in children <1 year of age than in those >2 years of age.[19] Several other studies have found bacterial pneumonias occur at a later age as compared to non-bacterial.[6,7,9,18] In our study too, bacterial pneumonia was seen to occur at a later age than non-bacterial pneumonia (p=.007). The viruses responsible for causing pneumonia at <5 years of age are RSV, influenza, parainfluenza, adenovirus, rhinovirus, etc.[19-21] However we do not have the facilities for viral cultures, so we were unable to identify the viral etiology in our cases. Among the bacteria, Streptococcus pneumoniae is the commonest one causing pneumonia in children 3 weeks to 4 years of age while Mycoplasma pneumonia and C. pneumoniae cause disease in children >5 years of age.[19-21] Other less frequent organisms are group A streptococcus, Staphylococcus aureus, Haemophilus influenza type B, Moraxella catarrhalis,etc.[19-21] For detecting the etiological agent, blood culture is usually done but it seldom comes positive (<10% cases).[19] Diagnostic tests to detect the organism, apart from blood culture are lung tap, serologic tests, PCR, pleural fluid culture, cold agglutinin titres and viral cultures. We got a positive blood culture in 36 cases (5.5% of total cases; 12.6% of bacterial pneumonia group) and one positive pleural fluid culture for S. aureus. The commonest organisms isolated on blood culture were S. aureus (n=11) followed by Pseudomonas (n=5) and Enterobacter (n=4). Other organisms isolated were Klebsiella (n=3), Coagulase negative staphylococcus aureus (n=3), Citrobacter (n=3), E.coli, group A streptococcus, Acinetobacter, Salmonella typhi and paratyphii. In our study, the commonest organism isolated was S. aureus. Similarly in a study conducted in Timisoara, lower respiratory secretions were cultured in children with pneumonia and S. aureus was the most common gram positive organism detected, while Pseudomonas was the most common gram negative bacteria detected.[22] Their microbial spectrum was similar to ours. In our case we did not get S. pneumonia positivity. This could be because S. pneumoniae is seldom bacteremic and blood culture is positive in only 4-10% of cases.[19,20]

CONCLUSIONS

CRP is a better specific marker than NLR for differentiating bacterial and non-bacterial pneumonias in children of one to 60 months of age.

REFERENCES

1. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015;385(9966):430-40.

2. Ministry of Health and Population (MOHP) [Nepal], New ERA, and ICF International Inc. Nepal Demographic and Health Survey 2011. Kathmandu, Nepal: Ministry of Health and Population, New ERA, and ICF International, Calverton, Maryland. 2012

3. Andreola B, Bressan S, Callegaro S, Liverani A, Plebani M, Da Dalt L. Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. Pediatr Infect Dis J. 2007; 26(8):672-7.

4. Müller B,Harbarth S, Stolz D, Bingisser R, Mueller C, Leuppi J, et al. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community acquired pneumonia. BMC Infect Dis. 2007; 7:10.

5. Flood RG, Badik J, Aronoff SC. The utility of serum C-reactive protein in differentiating bacterial from non-bacterial pneumonia in children: a meta-analysis of 1230 children. Pediatr Infect Dis J. 2008;27(2):95-9.

6. Virkki R, Juven T, Rikalainen H, Svedström E, Mertsola J, Ruuskanen O. Differentiation of bacterial and viral pneumonia in children. Thorax. 2002;57(5):438-41.

7. Bekdas M, Goksugur SB, Sarac EG, Erkocoglu M, Demircioglu F. Neutrophil/Lymphocyte and C-reactive protein/mean platelet volume ratios in differentiating between viral and bacterial pneumonias and diagnosing early complications in children. Saudi Med J. 2014;35(5):442-7.

8. Haran JP, Beaudoin FL, Suner S, Lu S. C-reactive protein as predictor of bacterial infection among patients with an influenza-like illness. Amer J Emerg Med. 2013;31(1):137-44.

9. Elemraid MA, Rushton SP, Thomas MF, Spencer DA, Gennery AR, Clark JE. Utility of inflammatory markers in predicting the aetiology of pneumonia in children. Infect Dis. 2014; 79(4): 458-62.

10. Holub M, Beran O, Kaspříková N, Chalupa P. Neutrophil to lymphocyte count ratio as a biomarker of bacterial infections. Cent Eur J Med. 2012;7(2):258-61.

11. Vaidya AK, Wagle NM, Merchant SM. Use of CSF C-reactive protein in differentiating bacterial and non-bacterial meningitis. J Postgrad Med. 1987; 33(2): 58-60.

12. Peltola HO. C-reactive protein for rapid monitoring of infections of the central nervous system. Lancet. 1982;1(8279):980-2.

13. Mentis AF, Kyprianou MA, Xirogianni A, Kesanopoulos K, Tzanakaki G. Neutrophil-to-lymphocyte ratio in the differential diagnosis of acute bacterial meningitis. Eur J Clin Microbiol Infect Dis. 2016; 35(3): 397-403.

14. Yazici M, Özkisacik M, Öztan MO, Gürsoy H. Neutrophil/lymphocyte ratio in the diagnosis of childhood appendicitis. Turk J Pediatr. 2010;52(4):400-3.

15. Li X, Zhu M, Wang J. Clinical application of neutrophil/lymphocyte count ratio in the diagnosis of lung bacterial infection in the elderly. Zhonghua Yi Xue Za Zhi. 2015;95(18):1405-10.

16. de Jager CP, van Wijk PT, Mathoera RB, de Jongh-Leuvenink J, van der Poll T, Wever PC. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. Crit Care. 2010;14(5): R192.

17. Muangchana C. Factors associated with diagnosis of bacterial pneumonia in children of Northern Thailand. Southeast Asian J Trop Med Public Health. 2009; 40(3):563-9.

18. Moreno L, Krishnan JA, Duran P, Ferrero F. Development and validation of a clinical prediction rule to distinguish bacterial from viral pneumonia in children. Pediatr Pulmonol. 2006;41(4):331-7.

19. Harris M, Clark J, Coote N, Fletcher P, Harnden A, McKean M, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. Thorax. 2011;66(Suppl 2)ii1-23.

20. Kelly MS, Sandora TJ. Community acquired pneumonia. In: Kliegman RM, Stanton BF, St. Geme

JW III, Schor NF, Behrman RE, editors. Nelson Textbook of Pediatrics. 20th ed. Philadelphia (PA): Elsevier; 2016. p. 2088-2094e1.

21. McIntosh K. Community acquired pneumonia in children. N Engl J Med. 2002;346(6):429-37.

22. Brad GF, Sabau I, Boia M, Marcovici T, Craciun A, Nilima K, et al. Trends in bacterial pathogens of lower respiratory tract infections in children. Timisoara Med J. 2011; 61: 193-8.