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Neutrophil to Lymphocyte Ratio, Monocyte to Lymphocyte Ratio, Platelet to Lymphocyte Ratio as Predictor of Outcome in Children with Community Acquired Pneumonia

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Abstract: *Background*: Pneumonia is the leading cause of death in children. An easy and inexpensive diagnostic tool is needed in managing the disease effectively. Neutrophil lymphocytes ratio (NLR), monocyte lymphocytes (MLR), and platelet lymphocytes (PLR) have role in predicting outcome of adult community acquired pneumonia but data in pediatric population is still limited. *Objective*: To prove that peripheral blood examination could be use as predictor of outcome in pediatric patients with community-acquired pneumonia. *Methods*: This is an observational analytic study with a retrospective case control design, to know value of neutrophil lymphocytes ratio (NLR), monocyte lymphocytes (MLR), and platelet lymphocytes (PLR) as predictor of outcome in pediatric community-acquired pneumonia. The study was conducted using medical record data of hospitalized patient in the Pediatric Ward Prof. Dr. I.G.N.G Ngoerah Hospital from November 2020 to December 2021 with the consecutive sampling method. Data analysis was carried out using receiver operator characteristic curve to find the optimal cut-off value then continued with chi-square analysis. The significance level (α) of this study was set at a probability value (p) of less than 0.05. *Results*: This study involved 104 subjects, divided equally into survive and deceased groups. After adjustment of age, gender, nutritional status, and result of microbiology examination, increase in NLR value ≥ 2.47 had 67.98 times risk of death (95% CI 17.18-268.95; $p < 0.001$) with 86.5% sensitivity and 90.4% specificity, an increase in MLR value ≥ 0.32 had 11.96 times risk of death (95% CI 4.5-31.72; $p < 0.001$) with 75% sensitivity and 80.8% specificity, and an increase in PLR value ≥ 121.07 had 8.41 times risk of death (95% CI 3.15-22.49; $p < 0.001$) with 65.4% sensitivity and 82.7% specificity. *Conclusion*: The increase in neutrophil lymphocytes, monocyte lymphocytes, and platelet lymphocytes ratio were predictor of mortality in pediatric community-acquired pneumonia.

Keywords: Neutrophil to Lymphocyte Ratio, Platelet to Lymphocyte Ratio, Monocyte to Lymphocyte Ratio, Pneumonia

1. Introduction

Pneumonia is the leading cause of death in children under five years old. The strategy to reduce mortality due to pneumonia includes prevention with vaccination, proper diagnosis, and prompt treatment. The clinical manifestation of severe pneumonia in young patients is often unclear, so inexpensive and widely available diagnostic tool is expected to help in management [1]. With that modality, the handling of pneumonia case can be more effective and efficient especially in cases predicted to have poor outcome,

Study on adult pneumonia patients found that neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), and platelet to lymphocyte ratio (PLR) represent the ongoing inflammatory process [2-4]. The release of inflammatory mediators causes the number of neutrophils, monocytes, and platelets high in the peripheral circulation, while premature apoptosis of lymphocytes occurred. This process causes the increase of NLR, MLR, and PLR comparable with the degree of clinical severity. This increase

is in line with more advanced inflammatory markers such as procalcitonin or C-reactive protein so that they can be used to estimate outcome in pneumonia patients [2, 5]. Many studies on adult pneumonia patients have been carried out, but the data supporting these facts in the pediatric age group is limited. Therefore, this study was conducted to find significance of complete blood count examination in predicting outcome of community acquired pneumonia in children.

2. Materials and Method

A case control study was performed to evaluate the use of NLR, MLR, and PLR as predictor of outcome in children with community acquired pneumonia. Medical record data of hospitalized children with pneumonia in Prof. Dr. I.G.N.G Ngoerah Hospital, Bali, from November 2020 until December 2021 was collected. This study has been approved by the Ethics Committee of Faculty of Medicine, Udayana University.

Children with pneumonia age 2 months until 18 years old were consecutively chosen as sample. Deceased patient was labeled as case and survived patient was defined as control group. Patients must have data of complete blood count (CBC) examination from Prof. Dr. I.G.N.G Ngoerah Hospital to be included in the study. If during hospitalization patient had several CBC examinations, only single CBC result before deterioration included in the study. Other collected data were age, gender, nutritional status, and microbiology examination. Patients with major congenital anomaly, immunodeficiency, acute severe malnutrition, and incomplete medical record were excluded. Sample size was calculated for each independent variable at a two-tailed α of 0.05, power of 0.80 and the biggest sample size was chosen.

The variables were defined as follows: age was calculated when data collected. Gender was based on phenotype appearance. Diagnosis of pneumonia was established clinically using World Health Organization criteria [6]. Complete blood count examination was done using CELL-DYN Ruby Automated Hematology Analyzer. Value of NLR, MLR, and PLR were calculated as the absolute count of neutrophils, monocytes, and platelets divided by total count of lymphocytes obtained from CBC.

Statistical analysis was done using SPSS for Windows version 22.0. Data distribution was asymmetrical, descriptive data presented as median and percentage. Receiver operating characteristic (ROC) analysis was performed to identify a cut-off of NLR, MLR, and PLR. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated between rise of NLR, MLR, PLR above cut-off with mortality. Comparison of various parameters between deceased and survived was done using chi square test. Multivariate analysis using logistic regression test was performed to find relationship between variables. Results were presented as odds ratio (OR) and 95% confidence interval (CI). P-value of <0.05 was considered significant.

3. Result

Of the 126 children hospitalized with community acquired pneumonia during study period, as many as 18 children were excluded because had major congenital anomaly and 4 children had severe acute malnutrition. Total sample was 104 patients divided equally into deceased (case) and survived (control) group. Most subjects in both groups were male with well-nourished nutritional status. Subjects in control group had higher leukocyte, absolute neutrophile, monocyte, and platelet count, while absolute lymphocyte count was lower compared to survived group. Deceased patient also had higher NLR, MLR, and PLR value (Table 1).

Table 1. *Characteristics of research subjects.*

Parameter	Deceased (n=52)	Survived (n=52)
Age, month, median (min-max)	12,5 (2-215)	9 (2-178)
Sex, male, n(%)	27 (51.9)	29 (55.8)
Nutritional status, n(%)		
Malnourished	18 (34.6)	10 (19.2)
Well-nourished	28 (53.8)	23 (44.2)
Overweight	6 (11.6)	19 (36.6)
Bacteria culture examination, n(%)	41 (78.8)	43 (82.7)
Positive result, n(%)	24 (46.2)	12 (23.1)
Leukocyte, median (min-max)	18.29 (6.78-70.15)	11,43 (2.36-41.21)
Neutrophile, median (min- max)	14.03 (2.04-67.23)	4,74 (0.59-20.5)
Monocyte, median (min- max)	1.34 (0.29-12.96)	0,95 (0.14-6.91)
Platelet, median (min- max)	381.5 (8.63-646)	352,5 (37-1035)
Lymphocyte, median (min- max)	2.21 (0.36-14.89)	4.78 (0.66-14.29)
NLR, median (min- max)	4.87 (0.06-95,86)	1.15 (0.1-3.66)
MLR, median (min- max)	0.62 (0.1-8.68)	0.21 (0.06-1.08)
PLR, median (min- max)	166.31 (0.79-1502.33)	75.66 (17.35-412.35)

NLR=neutrophil to lymphocyte ratio, MLR=monocyte to lymphocyte ratio, PLR=platelet to lymphocyte ratio, min=minimum, max=maximum

Bacteria culture examination was done in most subjects with positive result in 24 and 12 patients of deceased and survived groups, respectively. Most isolated bacteria in both groups are bacteria those commonly found in nosocomial infection (Table 2).

Table 2. *Bacteria from microbiology examination.*

Deceased (n)	Survived (n)
Pseudomonas aeruginosa (3)	
Staphylococcus aureus	
Staphylococcus haemolyticus	
Staphylococcus hominis ssp hominis (3)	
Staphylococcus epidermidis	
Methicillin-resistant *Staphylococcus epidermidis* (2)	Methicillin-resistant *Staphylococcus epidermidis*
Salmonella ssp	*Enterobacter cloacae ssp cloacae*
Acinetobacter lwoffii	Contaminant:
Enterobacter cloacae ssp cloacae	*Staphylococcus coagulase negative* (4)
Pseudomonas stutzeri	*Staphylococcus hominis ssp hominis*
Acinetobacter baumanii multidrug resistant organism	*Acinetobacter baumanii*
Klebsiella pneumonia ssp pneumonia	*Staphylococcus haemolyticus* (2)
Methicillin-resistant *Staphylococcus aureus*	*Staphylococcus epidermidis* (2)
Eschericia coli	
Contaminant:	
Acinetobacter lwofii (2)	
Staphylococcus coagulase negative (2)	
Bacillus ssp	

Receiver operating characteristic analysis showed that optimal cutoff value of NLR, MLR, and PLR to predict mortality were 2.47, 0.32, and 121.07 respectively. Complete result of ROC analysis was shown in Table 3.

Table 3. *The value of indicators in predicting mortality.*

	AUC	95% CI	*P*-value	Optimal cutoff value	Sensitivity (%)	Specificity (%)
NLR	0.907	0.841-0.972	<0.001	2.47	86.5	90.4
MLR	0.852	0.778-0.927	<0.001	0.32	75	80.8
PLR	0.757	0.662-0.852	<0.001	121.07	65.4	82.7

Bivariate and multivariate analysis of mortality prediction for patient with community acquired pneumonia were done using chi square and multivariate logistic regression (Table 4). Clinical variables with difference more than 15% in characteristics (nutritional status and positive culture result) were included in the multivariate logistic regression analysis to identify the independent predictors of mortality. Positive culture examination affected relationship between PLR and mortality (P 0.04) while NLR and MLR were unaffected (P >0.05).

Table 4. *Univariate and multivariate analysis of mortality prediction.*

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
NLR	60.43 (17.87-204.33)	<0.001	67.98 (17.18-268.95)	<0.001
MLR	12.6 (4.96-32.02)	<0.001	11.96 (4.5-31.72)	<0.001
PLR	9.03 (3.6-22.59)	<0.001	8.41 (3.15-22.49)	<0.001

4. Discussion

In this retrospective study, we confirmed the importance of prognostic biomarkers using simple complete blood count examination in children with community acquired pneumonia (CAP). Complete blood count examination is inexpensive and widely available in both inpatient and outpatient settings. This is important because pneumonia is mostly found in disadvantaged area with limited diagnostic tool. Three different biomarkers were evaluated to estimate outcome in CAP. The result of this study adds evidence in pediatric age group while study in this specific population is still limited.

Pneumonia in this study was found to be more common in male children (56 out of a total of 104 subjects) with the median age in both groups is under 24 months. These results are in line with the results of a population-based study from Spain which found that the incidence of community pneumonia leading to hospitalization was higher in boys than girls with a ratio of 1.05. Most of the children admitted were children under 2 years of age, with the rate of hospitalization decreasing with age advancement [7].

Majority of subjects had good nutritional status. In the deceased group, the proportion of malnourished patient was greater compared to children who survived. These data are in accordance with study by Assfaw et al. who found that nutritional status affects outcomes in pediatric patients treated for pneumonia [8]. Children with poor nutritional status require longer hospitalization to recover and have a higher risk of death than children with good nutritional status.

Clinical manifestations in pneumonia are the result of a complex interaction between host, pathogen, and environmental factors. Only a small proportion of blood culture examinations in pneumonia patients have isolated the

causative organism. Although not applicable in most settings, microbiological examination to find the etiology of pneumonia cases still important considering the increase of antibiotic resistance. Culture examination of the deceased patient succeeded in isolating bacteria in 24 of 41 samples (59%) with 5 of them identified as contaminants. This figure was higher than in the survived patient. Overall examination of blood cultures isolated 15 pathogenic bacteria (14.4%) and examination of sputum cultures isolated 4 pathogenic bacteria. Our result is greater than the study by Negash et al [9], which obtained 6.19% positive blood cultures in patients with pneumonia. The most isolated bacteria in this study were Pseudomonas aeruginosa, Staphylococcus hominis ssp hominis, and methicillin-resistant Staphylococcus epidermidis. We suspect the patients were infected during the duration of treatment or from a referring hospital because these bacteria are the cause of nosocomial infections. Nosocomial infections are associated with high rates of morbidity and mortality.

We found that CBC derived parameters NLR, MLR, and PLR could have prognostic value predicting mortality in pediatric CAP. Various studies used different cutoff to predict mortality, values such as 5.27 (94.1% sensitivity 29% specificity) or 9 (70% sensitivity 91.2% specificity) for NLR, 0.9 (55.3% sensitivity 81.4% specificity) for MLR, and 211.6 for PLR [3, 5, 10]. In the present study, we found optimal cutoff value for NLR, MLR, and PLR were 2.47, 0.32, and 121.07 respectively. Based on the ROC analysis, the AUC of NLR was the largest followed by MLR and PLR. Neutrophile to lymphocyte ratio also had highest sensitivity and specificity. Meanwhile, MLR and PLR have high specificity (80.8% and 82.7%) and rather low sensitivity (75% and 65.4%). The high specificity indicated that majority of patients who died have higher NLR, MLR, and PLR value.

During inflammation or infection, activation of various inflammatory cells and release of cytokine cause recruitment of neutrophils, monocytes, and platelet, along with driven apoptosis of lymphocytes [11-14]. These mechanisms were hypothesized causing increase in the NLR, MLR, and PLR. Thus, NLR, MLR, and PLR can also serve as simple indicator of the severity of the systemic inflammation. Study also showed that increase in NLR, MLR, and PLR is associated with higher mortality risk [3-5]. In our study, value of NLR, MLR, and PLR above cutoff would be a marker of increased risk of death with an OR of 67.98 (95% CI 17.18-268.95), 11.96 (95% CI 4.5-31.72), 8.41 (95% CI 3.15-22.49) respectively, after adjustment for nutritional status and positive culture result.

Despite our effort, this study has several limitations. This single center study was conducted in a tertiary public hospital serves as referral center that treats pneumonia with various comorbidities, so the result may be different if a similar study is carried out to different populations. Second, the sample considered to be rather small, had a wide range of age, and were not homogeneous resulting wide confidence interval although it was enough to show statistically significant result. Prospective design in large multi-center study may validate our findings in the future.

5. Conclusion

The increase in neutrophil lymphocytes, monocyte lymphocytes, and platelet lymphocytes ratio could be use as predictor of mortality in pediatric community-acquired pneumonia. Neutrophil lymphocyte ratio has better performance than the other two parameters. Future studies with large samples and prospective design are needed to confirm these findings.

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