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The Neutrophil-Lymphocyte Count Ratio in Patients with Community-Acquired Pneumonia

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ABSTRACT:-
Objective: The neutrophil-lymphocyte count ratio (NLCR) has been identified as a predictor of bacteremia in medical emergencies. The aim of this study was to investigate the value of the NLCR in patients with community-acquired pneumonia (CAP).
Methods: Consecutive pediatric patients were retrospectively studied from those admitted to PICU and few of those admitted to ward. Pneumonia severity (PICU admission), clinical characteristics, complications and outcomes were related to the NLCR and compared with C-reactive protein (CRP), neutrophil count, white blood cell (WBC) count. The study cohort consisted of 50 patients diagnosed with CAP. 72% (36/50) patients admitted to PICU were studied and 28% (14/50) were admitted in ward. The NLCR was calculated.
Results: NLCR was significantly more in ICU admitted patients(p=0.026)
Conclusion: Admission NLCR at the emergency department predicts severity and outcome of CAP with a higher prognostic accuracy as compared with traditional infection markers.

Keywords - neutrophil-lymphocyte ratio,pediatric,PICU,pneumonia,CRP

I. INTRODUCTION

Community-acquired pneumonia (CAP) is a common infection that is potentially deadly[1,2]. One of the objectives in the care of CAP patients at the time of diagnosis is to establish an estimated prognosis, in order to determine the need for hospitalization or for planning the most suitable follow-up.It is one of the most common causes for death in under 5. Numerous scales for assessing CAP severity and risk are available for this purpose, such as the, the Pneumonia Severity Index (PSI)[3], and the Severe Community Acquired Pneumonia (SCAP) score[4]. These scales have been widely validated in large population cohorts and are currently the most useful tools available for assessing the prognosis of CAP patients at the time of diagnosis[5].

In Immuno-competent patients, white blood cell populations play an important role in the systemic inflammatory response to infection.Following endotoxemia the number of circulating neutrophils increases while lymphocyte counts decrease. The occurence of Neutrophilia is well recognized as infection marker. Absolute lymphocytopenia (lymphocyte count below 1.0610e9/l) as a possible marker in infectious disease management is not routinely considered. Absolute lymphocytopenia is considered recently in several conditions nowadays.Combining both parameters seems a logical step and the ratio of neutrophil and lymphocyte counts is increasingly used in several clinical circumstances. Initially, this so-called neutrophil-lymphocyte count ratio (NLCR) was studied as an infection marker in ICU patients in adults and found to correlate well with disease severity and outcome, according to APACHE-II and SOFA scores[6]. Other studies focused on the use of the NLCR in specific clinical conditions, like appendicitis, or its use as an independent predictor of survival in patients with various conditions ranging from oncological to cardiovascular diseases[7,8,9,10]. In a retrospective study, the NLCR proved to be a simple and even better marker in predicting bacteremia than routine parameters, like white blood cell (WBC) count and C-reactive protein (CRP) level, in infectious emergency admissions[11]. As CAP is an important reason for Emergency Department (ED) admission and subsequent hospitalization, we retrospectively studied the prognostic value of NLCR in patients with this condition.

Efforts are currently underway to improve the prognostic value of these clinical scales. Given that pneumonia is a localized infectious process that causes a systemic inflammatory response, it is postulated that the study of this inflammatory process would assist in evaluating the severity of CAP and predicting its progress. In this respect, several biomarkers determined at the time of CAP diagnosis have been studied, including procalcitonin (PCT), proadrenomedullin (proADM) and copeptin[12,13]; these molecules measured at diagnosis have shown a greater prognostic power than C-reactive protein (CRP) or total leukocyte count, but have not proven to be superior to traditional scales. Several authors have reassessed the use of simpler, more

accessible markers at diagnosis, such as the neutrophil/lymphocytes ratio (NLR)[11,14] or the neutrophil count percentage (NCP)[14],with the advantage that both are easily identifiable, inexpensive parameters.

Along these lines,Curbelo et al.[14] compared NCP with PCT, proADM, and copeptin, and found it was not significantly inferior in terms of its prognostic capacity for mortality in the short and medium term.Continuing in the search for efficient biomarkers, other authors have proposed simple, economic parameters and evaluated their usefulness not only for diagnosis, but also for the follow-up of patients with CAP.

Zhydkov et al. found that total leukocyte counts and CRP in patients hospitalized for CAP provided prognostic information if they were evaluated in clinical laboratory tests during patient follow-up[15]. Other studies also show that NLR and NCP in early-stage blood tests (at 3–5 days) are equally or more useful than determinations made on admission[14], and suggest that these 2 parameters may be very useful prognostic markers of the progress of patients hospitalized for CAP.The aim of this study was to evaluate the usefulness of NLCR measured during the course of CAP, and their role as predictors of morbidity and mortality.

II. MATERIALS AND METHODS

This was a retrospective study of CAP patients admitted to ward and PICU, department of pediatrics, jan 2019 to aug 2019. The study protocol was approved by the Clinical Research Ethics Committee of the same center.

The inclusion criteria were: age<18 years at the time of diagnosis and hospitalization for CAP in the departments of pediatrics.We determined that both the admission and discharge reports listed the primary diagnosis as CAP, and the presence of lower respiratory tract symptoms (cough, expectoration, dyspnea, tachypnea or pleuritic pain) and the appearance of a new infiltrate on X-ray without any other justifiable cause. Total leukocytes and differential counts were determined from peripheral blood in EDTA, and by fluorescence flow cytometry and hydrodynamic focusing (forward and side scatter with a Sysmex XE-2100TM automated hematology analyzer (Sysmex, Kobe, Japan).

We excluded patients who did not receive antibiotics in the context of a decision to limit treatment. Other exclusion criteria included the presence of active hematologic or oncologic disease and severe immunodeficiency.

All patients were classified using socio-demographic characteristics, comorbidities, and treatment were systematically recorded. In addition, clinical, radiological, and laboratory variables associated with the CAP episode were recorded. Patients were treated according to the routine clinical practice. The main outcome variable was NLCR and correlation to WBC, CRP,ESR.

1.1Statistical Methods:

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, Assumptions: 1.Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, Cases of the samples should be independent

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven`s test for homogeneity of variance has been performed to assess the homogeneity of variance.

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Fisher Exact test used when cell samples are very small.

Pearson correlation between study variables is performed to find the degree of relationship, Pearson correlation co-efficient ranging between -1 to 1, -1 being the perfect negative correlation, 0 is the no correlation and 1 means perfect Positive correlation

A. Significant figures

+ Suggestive significance (P value: $0.05<P<0.10$)
* Moderately significant (P value:$0.01<P \leq 0.05$)
** Strongly significant (P value : $P \leq 0.01$)

II. RESULTS AND ANALYSIS

Table 1: Age distribution of patients studied

Age in years	No. of patients	%
Up to 1yr	19	38.0
1-2yrs	7	14.0
3-5yrs	17	34.0
6-10yrs	4	8.0
>10yrs	3	6.0
Total	50	100.0

Most of the patients included were in the age group of <1yr and most others belonged to 3-5 years.(fig1)

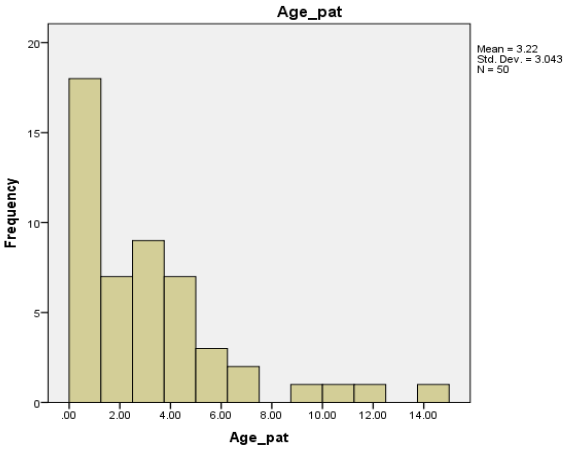

Fig 1: age distribution

Table 2: Gender distribution of patients studied

Gender	No. of patients	%
Female	22	44.0
Male	28	56.0
Total	50	100.0

Study included 44% of females and rest were males

Table 3: Blood investigations

variables	No. of patients (n=50)	%
Hemoglobin (g/dl)		
• <12	38	76.0
• 12-16	12	24.0
• >16	0	0.0
PCV		
• <30	13	26.0
• 30-40	34	68.0
• >40	3	6.0
Total Count		
• <4000	2	4.0
• 4000-11000	19	38.0
• >11000	29	58.0

About 76% of the patients had Hb <12 g/dL. Most of the patients had elevated total counts of >11,000 c/mm^3.

Table 4: CBC variables

	No. of patients (n=50)	**%**
Neutrophils		
• <50	10	20.0
• 50-90	38	76.0
• >90	2	4.0
Lymphocytes		
• <30	24	48.0
• 30-60	24	48.0
• >60	2	4.0
Monocytes		
• <3	14	28.0
• 3-6	26	52.0
• >6	1	2.0
• NA	9	18.0
Basophils		
• 0	2	4.0
• NA	48	96.0
Eosinophils		
• 0	1	2.0
• 1	5	10.0
• 2	8	16.0
• 3	5	10.0
• 4	2	4.0
• 5	3	6.0
• NA	26	52.0

Patients had predominant neutrophil count. 80% of the patients had neutrophilia. Lymphocytopenia was seen in 48% of the patients.

Table 5: Platelet count, ESR, NLCR and CRP

	No. of patients (n=50)	**%**
Platelet Count		
• <4	32	64.0
• 4-7	15	30.0
• >7	3	6.0
ESR		
• <50	37	74.0
• 50-100	9	18.0
• >100	4	8.0
NLCR		
• <2	24	48.0
• 2-4	10	20.0
• >4	16	32.0
CRP		
• <10	11	22.0
• 10-20	24	48.0
• >20	15	30.0

Elevated ESR was seen in 37 patients. 26% patients had ESR of >50mm/hr

Table 6: ICU stay distribution of patients studied

ICU	No. of patients	%
No	15	30.0
Yes	35	70.0
Total	50	100.0

35 patients required PICU admission out of 50.

Table 7: Comparison of clinical variables according to ICU stay of patients studied

variables	ICU		P value
	No	Yes	
Hemoglobin (g/dl)	12.08±1.38	9.49±1.87	<0.001**
PCV	36.51±3.94	30.79±5.82	0.001**
Total Count	9247.93±2506.02	16377.43±7870.95	0.001**
Neutrophils	60.07±13.32	67.40±18.46	0.171
Lymphocytes	35.27±13.2	28.77±17.63	0.207
Monocytes	2.83±1.70	3.41±2.13	0.407
Basophils	3.00±1.41	2.00±1.22	0.077+
Eosinophils	2.65±0.84	3.98±1.77	0.008**
Platelet count	17.13±7.90	45.43±38.17	0.007**
ESR	2.45±2.50	4.30±4.08	0.112
NLCR	12.73±9.48	22.12±14.55	0.026*
CRP	12.08±1.38	9.49±1.87	<0.001**

Total count was elevated significantly in patients requiring PICU admission. Average total count of icu admitted patients was 16377(p=0.001)

Neutrophil count was not significantly different in either groups.

NLCR was significantly more in ICU admitted patients(p=0.026).CRP was more in patients not requiring ICU in our study.

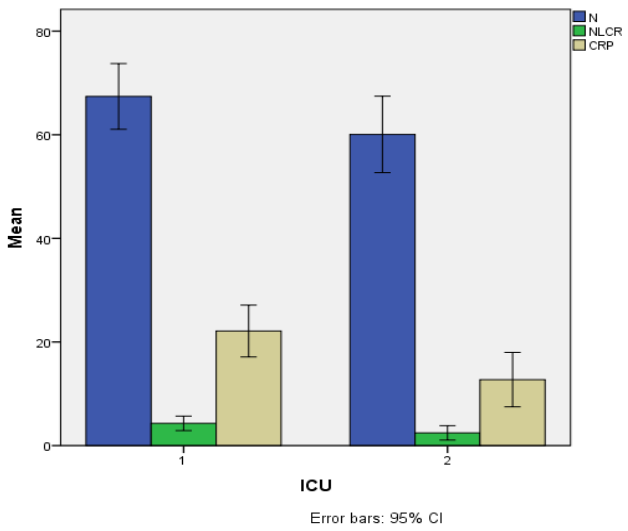

Fig 2: ICU admission with inflamatory markers correlation

Table 8: Pearson correlation

Pair	r value	P value
CRP **vs** Total Count	0.107	0.460
CRP **vs** Neutrophils	0.006	.0965
CRP **vs** Lymphocytes	0.004	0.978
CRP **vs** ESR	-0.042	0.771
CRP **vs** NLCR	0.046	0.751

Correlation coefficient of CRP was seen here. There was non significant positive correlation between CRP and total count. CRP and NLCR did not correlate to well.

Table 9: Pearson correlation

pair	r value	P value
NLCR **vs** Total Count	0.577	<0.001**
NLCR **vs** Neutrophils	0.848	<0.001**
NLCR **vs** Lymphocytes	-0.827	<0.001**
NLCR **vs** ESR	0.229	0.110

NLCR had good correlation with total count($p<0.001$), neutrophils($p<0.001$) and negatively correlated with lymphocytes($p<0.001$)(fig3)

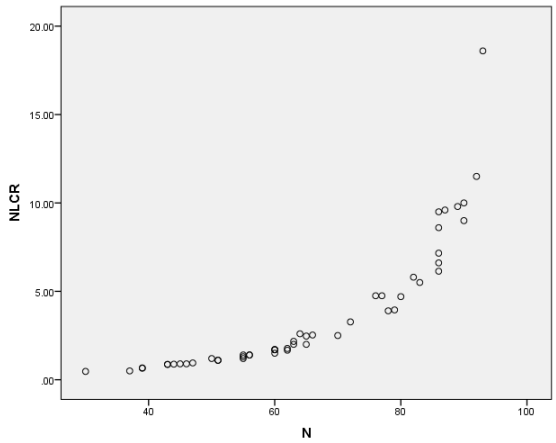

Fig 3: NCLR vs Neutrophil count

III. DISCUSSION

Recently, the NLCR has been ‘‘rediscovered’’ as a simple, promising marker in several clinical circumstances. The discriminatory capacity of the NLCR in CAP patients outweighed predictivevalues of traditional biomarkers. Increased NLCR values were seen in patients with increased ICU admission. The AUC of the NLCR.ROC curve was significantly higher than that of conventional markers, especially CRP, in predicting mortality in CAP patients.The host inflammatory response in the development of pneumonia has gained growing interest and infection markers are increasingly used to facilitate treatment decisions and improve the accuracy of clinical severity scores in patients admitted with CAP. ‘‘Old’’ markers like CRP, WBC count and neutrophil count are still the most frequently used infection markers in daily clinical practice. Although recently introduced infection markers such as procalcitonin, several cytokines and markers like endothelin-1, copeptin and pro-adrenomedullin show promising results in risk assessment and outcome prediction the implementation of these ‘‘new’’ infection markers is hampered by validation, costs and accessibility.In various stressful events the physiological response of circulating leucocytes is characterized by

an increase in neutrophil counts and a decline in lymphocyte counts. Neutrophilia is caused by demargination of neutrophils, delayed apoptosis of neutrophils and stimulation of stem cells by growth factors. Margination of lymphocytes, redistribution of lymphocytes and marked accelerated apoptosis are supposed mechanisms of the observed lymphocytopenia in infectious emergencies.

Lymphocytopenia has shown promising results in the prediction of bacteremia in infectious emergency admissions. Although relatively unknown as a marker of disease severity or prognosis, lymphocytopenia has been described in several forms of CAP, especially in the acute phase and probably limited to T-cellsand T-cell subsets. In CAP patients it is hypothesized that depression of absolute peripheral blood T-cell counts represents the shift of these cells towards the lung in order to be sequestered in protective mechanisms. The mean lymphocyte count in our overall study population was just above the lower limit of normal.

In the current retrospective study, we further explored the value of the NLCR in patients admitted with CAP.

Our current study adds to the value of the NLCR by showing that this marker is of interest in patients admitted to the ED with CAP. In our opinion the novelty of the NLCR is the possibility of implementing this parameter simply by using already available biomarkers (WBC-count, neutrophil count and lymphocyte count). Since calculating the NLCR is easy to do and does not require additional testing it may add to our ability to predict mortality. Diagnosing community-acquired pneumonia and subsequently assessing prognosis, severity and site-of-care indicators remains a challenging process.

It could be of interest to investigate whether adding the NLCR to currently existing severity scores would improve the overall performance of these scores thereby assisting the emergency physician in the treatment options. Use of the NLCR may allow the clinician to stratify patients with CAP into different prognostic categories and could possibly add to the performance of wellaccepted severity-of-illness scores.This study has several limitations. First, in view of the minor differences between the AUC for neutrophil numbers and NLCR, the NLCR may simply reflect differences in neutrophil numbers.Second, as this is a single centre study the results should be validated in other settings. Third, recently developed infection markers (procalcitonin, pro-adrenomedullin, neopterin) were not evaluated. Fourth, in general biomarkers alone are clearly less suited in the prediction of prognosis and severity of disease.

IV. CONCLUSION

NCP and NLR are accessible, inexpensive parameters that provide information on the prognosis of patients with severe CAP when analyzed in early follow-up.NLCR proved to be a simple and even better marker in predicting bacteremia than routine parameters, like white blood cell (WBC) count and C-reactive protein (CRP) level, in infectious emergency admissions.

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