ORIGINAL ARTICLE

Evaluation of Neutrophil to Lymphocyte Ratio as a Biomarker in Children with Exacerbated Asthma

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Abstract

Background: ***Asthma is a chronic inflammation of the airways, defined by varying respiratory symptoms and variable expiratory airflow limitations, which may become persistent over time.***

Aim: ***To evaluate correlation between neutrophil to lymphocyte ratio (NLR) and asthma exacerbation and how we can use them as biomarkers.***

Patients and methods: ***This was a case-control study has been carried out on 150 participants, divided into two groups. The first group included 100 asthmatic kids presenting with acute exacerbations of asthma. The second group included 50 apparently healthy kids presenting to the outpatient clinic who served as the control group at Bab Al-Sharia University Hospital.***

Results: ***The AUC for the absolute neutrophil count was 1 (p-value less than 0.001), indicating a perfect predictive ability. The optimal cutoff point for the absolute neutrophil count was 2.65, with 100% sensitivity and a 63% specificity. The AUC for the absolute lymphocyte count was 0.17 (p-value less than 0.001), indicating a poor predictive ability. The optimal cutoff point for the absolute lymphocyte count was 2.35, with 40% sensitivity and 97% specificity. The AUC for the neutrophil-to-lymphocyte ratio was 1 (p-value less than 0.001), indicating a perfect predictive ability. The optimal cutoff point for the neutrophil-to-lymphocyte ratio was 0.95, with 100% sensitivity and 91% specificity.***

Conclusion: ***The neutrophil to lymphocyte ratio and PLR were significantly elevated throughout acute asthma exacerbations in kids. The results indicate that these variables may serve as markers for acute exacerbation in childhood asthma cases.***

Keywords: NLR; exacerbated asthma; biomarkers

1. Introduction

Asthma is a heterogeneous illness typically marked by chronic airway inflammation. The illness is characterized by a history of respiratory symptoms, including wheezing, chest tightness, and dyspnea, which change over time and in severity, accompanied by varying expiratory airflow limitation that can eventually turn persistent.[1]

Asthma is among the most prevalent chronic illnesses in kids. It's characterized by a history of respiratory symptoms, including wheezing, chest tightness, and dyspnea, which change over time and in severity, accompanied by varying expiratory airflow limitation. Cases might encounter episodic exacerbations of asthma that might be life-threatening and impose significant burdens on both cases and the community.[2]

Alongside the characteristic chronic airway inflammation, which is considered the primary pathogenic feature of asthma, systemic inflammation is additionally observed in asthma cases.[3]

The elevated levels of pro-inflammatory cytokines, including interleukin (IL)-6 and tumor necrosis factor-α (TNF-α), contribute to this inflammation. In asthmatic cases, these pro-inflammatory cytokines are elevated in immune cells, including neutrophils and natural killer cells, and promote hepatic synthesis of acute-phase proteins, like C-reactive protein (CRP).[4]

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Evidence indicates that eosinophils and neutrophils are primary cells involved in asthma pathology, with neutrophils being more common in severe cases of asthma.[5]

Asthma exacerbations are episodes marked by a worsening of symptoms such as shortness of breath, cough, wheezing, or chest tightness, accompanied by a reduction in lung function. Eosinophils and neutrophils in the blood are both related to the prevalence of asthma exacerbations. Recent investigations indicate that eosinophil counts in blood and sputum may serve as predictors of asthma exacerbation.[6]

An elevated eosinophil count in the blood may serve as a risk factor for asthma exacerbations. Understanding the inflammatory mechanisms of exacerbations may help formulate prevention and management strategies.[7]

The neutrophil-lymphocyte ratio serves as an indicator of systemic inflammation. The mean neutrophil-to-lymphocyte ratio is elevated in asthma cases, particularly in those with unstable asthma, compared to healthy individuals. The neutrophil-lymphocyte ratio assay may aid in distinguishing asthma exacerbations by assessing the impact of inflammation on asthma and its worsening in exacerbation.[8]

This work aimed to assess correlation among neutrophil to lymphocyte ratio and asthma exacerbation and how we can use them as biomarkers.

2. Patients and methods

This was a case-control investigation on a total of 150 participants, divided into two groups. The first group included 100 asthmatic kids presenting with acute exacerbations of asthma. The second group included 50 apparently healthy kids presenting to the outpatient clinic who served as the control group at Bab Al-Sharia University Hospital, which houses facilities equipped for comprehensive pediatric asthma care, including an emergency department, allergy unit, outpatient clinic and Pulmonary Functions Laboratory.

Inclusion Criteria:

Controls: Included were kids aged 5 to 18 years with no history or evidence of allergic illnesses like allergic rhinitis, asthma, or eczema, nor any signs of infection. These kids also met none of the exclusion criteria.

Cases: This group included kids aged 5 to 18 years who: Attended the emergency department and were diagnosed with bronchial asthma by a certified pulmonologist and followed up in the allergy unit. Presented with an acute asthma exacerbation requiring at least one nebulization of a B2 agonist. Included both males and females.

Exclusion Criteria: Kids with any systemic illness like renal, hepatic, cardiovascular diseases, neoplasms, diabetes mellitus, or systemic inflammatory disorders. Kides have been diagnosed with a chest infection at the time of study enrollment. Kids on long-term systemic corticosteroid medication.

Methods:

Pediatric Respiratory Assessment Measure (PRAM) Score:

Assessment Protocol: The PRAM score was determined in the emergency department using a standardized scoring system that evaluates respiratory signs including wheezing, use of accessory muscles, oxygen saturation, and heart rate. kids were categorized as having mild (score 0-3), moderate (score 4-7), or severe (score 8-12) asthma exacerbations based on their PRAM scores.

Complete Blood Picture:

Blood Collection: Blood samples were collected from a peripheral vein using aseptic techniques.

Laboratory Analysis: Automated hematological analyzers were used to count neutrophil and lymphocyte populations. NLR has been determined by dividing the absolute neutrophil count by the absolute lymphocyte count.

C-reactive Protein (CRP)

Sample Collection and Analysis: Blood samples for CRP were drawn concurrently with those for the complete blood picture. CRP was measured using high-sensitivity assays capable of detecting low levels of inflammation, which are crucial for correlating with asthma exacerbations.

Chest X-ray

Procedure: Chest X-rays were performed to identify any underlying pulmonary conditions that could exacerbate asthma symptoms, such as pneumonia or atelectasis. Radiographs were interpreted by a pediatric radiologist blind to the patient's clinical status.

Spirometry

Test Protocol: Spirometry has been conducted according to the standards set by the American Thoracic Society. Measurements of forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were taken.

Follow-up testing: Post-bronchodilator spirometry was conducted 15 minutes after administering a bronchodilator to evaluate the reversibility of airway obstruction, an important characteristic of asthma.

3. Results

A statistically insignificant distinction has been observed among two investigated groups regarding age and sex (Table 1).

Table 1. Demographic Data of Study Groups

		CASES GROUP (NUMBER=100)	CONTROL GROUP (NUMBER=50)	P-VALUE
AGE (YEAR)	Mean ±SD	9.98±3.49	10.96±2.51	0.261
SEX	Male No (%)	52 (52%)	27 (54%)	0.887
	Female No (%)	48 (48%)	23 (46%)	

The cases group had a significantly higher mean white blood cell (WBC) count than the control group (10.61±3.37 versus 6.82±1.5, p-value less than 0.001). Similarly, the cases group had a significantly higher absolute neutrophil count (7±1.7 versus 2.69±1.5, p-value less than 0.001) and a significantly lower absolute lymphocyte count (2.24±0.48 versus 27±0.24, p-value less than 0.001) than the control group. The cases group also had a significantly higher platelet count (296.63±67.88 versus 300.17±49.93, p-value less than 0.001) and a significantly higher C-reactive protein level (6.87±1.9 versus 1.87±0.58, p-value less than 0.001) than the control group. Nevertheless, insignificant distinctions have been observed among both groups regarding hemoglobin, total protein, and albumin levels. The cases group had a significantly higher neutrophil-to-lymphocyte ratio (3.45±1.75 versus 1±0.13, p-value less than 0.001) and platelet-to-lymphocyte ratio (126.81±43.76 versus 110.58±10.14, p-value less than 0.001) than the control group (Table 2).

Table 2. Laboratory data of study groups

	CASES GROUP (NUMBER=100)	CONTROL GROUP (NUMBER=50)	P-VALUE
	Mean ±SD	Mean ±SD	
WBC (10^9/L)	10.61±3.37	6.82±1.5	< 0.001*
ABSOLUTE NEUTROPHIL COUNT (10^9/L)	7±1.7	2.69±1.5	< 0.001*
ABSOLUTE LYMPHOCYTE COUNT (10^9/L)	2.24±0.48	27±0.24	< 0.001*
HEMOGLOBIN (G/L)	13.25±12.82	13.89±12.45	0.721
PLATELET (10^9/L)	296.63±67.88	300.17±49.93	< 0.001*
C-REACTIVE PROTEIN (MG/L)	6.87±1.9	1.87±0.58	< 0.001*
TOTAL PROTEIN (G/L)	69.43±5.1	69.31±4.37	0.859
ALBUMIN (G/L)	42.99±3.5	43.52±2	0.012*
NEUTROPHIL-TO-LYMPHOCYTE RATIO	3.45±1.75	1±0.13	< 0.001*
PLATELET-TO-LYMPHOCYTE RATIO	126.81±43.76	110.58±10.14	< 0.001*

*p-value is significant

Table presents the comparison of FEV1 and FEV1/FVC ratio among the cases and control groups. The cases group had a significantly lower mean FEV1 (71.67±8.37) than the control group (78.84±1.52, p-value less than 0.001). Similarly, the cases group had a significantly lower mean FEV1/FVC ratio (86.15±13.85) than the control group (95±0.00, p-value less than 0.001).

Table 3. Comparison between Both Groups Regarding FEV1 and FEV1 /FVC Ratio

	CASES GROUP (N=100)	CONTROL GROUP (N=50)	P-VALUE
	Mean ±SD	Mean ±SD	
FEV1	71.67±8.37	78.84±1.52	< 0.001*
FEV1 /FVC RATIO	86.15±13.85	95±0.00	< 0.001*

FEV1: forced expiration volume in one second; FVC: forced vital capacity. *p-value is significant

Table 4 presents the distribution of the cases group according to the PRAM score. Out of the 100 cases, 63 (63%) have been classified as mild, 20 (20%) as moderate, and 17 (17%) as severe.

Table 4. Distribution of Cases Group According to PRAM Score

	CASES GROUP (NUMBER=100)
	No (%)
MILD	63 (63%)
MODERATE	20 (20%)
SEVERE	17 (17%)

Table 5 presents that there was significant relation between severity and Age, WBC, Absolute lymphocyte count, Absolute neutrophil count, Platelet, Total Protein, Albumin, C-reactive protein, NLR, PLR, FEV1 and FEV1 /FVC ratio.

Table 5. Comparison between mild, moderate and severe groups

	MILD GROUP (NUMBER=63)	MODERATE GROUP (NUMBER=20)	SEVERE GROUP (NUMBER=17)	CONTROL GROUP (NUMBER=50)	P-VALUE
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	
AGE (YEAR)	7.74±1.31	12.8±2.39	14.94±2.5	10.96±2.51	< 0.001*
WBC (10^9/L)	9.64±2.85	12±4.08	12.52±3	6.82±1.5	< 0.001*
ABSOLUTE NEUTROPHIL COUNT (10^9/L)	5.95±0.86	8.53±1.61	9.16±0.72	2.69±1.5	< 0.001*
ABSOLUTE LYMPHOCYTE COUNT (10^9/L)	2.3±0.14	2.78±0.21	1.31±0.08	27±0.24	< 0.001*
HEMOGLOBIN (G/L)	11.62±0.74	12.03±0.66	20.72±30.71	13.89±12.45	0.152
PLATELET (10^9/L)	270.74±72.93	269.85±70.11	265±45.17	300.17±49.93	< 0.001*
C-REACTIVE PROTEIN (MG/L)	7.32±1.77	4.71±1.32	4.37±2.9	1.87±0.58	< 0.001*
TOTAL PROTEIN (G/L)	68.26±4.43	69.85±4.4	73.23±6.49	69.31±4.37	< 0.001*

ALBUMIN (G/L)	41.9±2.97	43.51±4.06	43.64±4.27	43.52±2	0.002 *
NEUTROPHIL-TO-LYMPHOCYTE RATIO	2.61±0.49	3.07±0.58	7.05±0.95	1±0.13	< 0.001*
PLATELET-TO-LYMPHOCYTE RATIO	115.63±26.21	98.4±30.38	201.64±24.69	110.58±10.14	< 0.001*
FEV1	76.68±2.48	69.65±3.21	55.47±3.82	78.84±1.52	< 0.001*
FEV1 /FVC RATIO	93.73±3.47	86.25±5.82	57.94±5.32	95±0.00	< 0.001*

*p-value is significant

Table 6 presents the outcomes of the univariate and multivariate analysis to determine predictors of asthma exacerbation. In the univariate analysis, the absolute lymphocyte count, hemoglobin level, total protein level, and albumin level were significantly correlated with asthma exacerbation (p-value less than 0.001 for all). Nevertheless, in the multivariate analysis, none of these variables were found to be significant predictors of asthma exacerbation (p=1 for all variables). The neutrophil-to-lymphocyte ratio and FEV1 were also significantly associated with asthma exacerbation in the univariate analysis (p-value less than 0.001 for both), but haven't been involved in the multivariate analysis.

Table 6. Univariate and Multivariate Analysis to Determine Predictors of Asthma Exacerbation

	UNIVARIATE ANALYSIS OR (95 CI)	P-VALUE	MULTIVARIATE ANALYSIS OR (95 CI)	P-VALUE
WBC (10^9/L)	0.988 (0.734-1.33)	0.935	-	-
ABSOLUTE LYMPHOCYTE COUNT (10^9/L)	0.000 (0.000-0.015)	< 0.001*	1 (0.000)	1
HEMOGLOBIN (G/L)	0.252 (0.131-0.488)	< 0.001*	0.1 (2.97-3.35)	1
TOTAL PROTEIN (G/L)	0.723 (0.628-0.834)	< 0.001*	1 (0.000)	1
ALBUMIN (G/L)	0.231 (0.12-0.44)	< 0.001*	1(0.000)	1
NEUTROPHIL-TO-LYMPHOCYTE RATIO	3.29 (0.000)	0.954	-	-
PLATELET-TO-LYMPHOCYTE RATIO	1.47 (1.17-1.85)	< 0.001*	1 (1.67-5.97)	1
FEV1	0.441(0.29-0.67)	< 0.001*	1 (0.000)	1
FEV1 /FVC RATIO	0.914 (0.745-1.12)	0.385	1 (0.000)	1

*p-value is significant

Table 7 presents the outcomes of the ROC analysis for the prediction of asthma exacerbation. The absolute neutrophil count, absolute lymphocyte count, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio were included in the analysis. The AUC for the absolute neutrophil count was 1 (p-value less than 0.001), indicating a perfect predictive ability. The optimal cutoff point for the absolute neutrophil count was 2.65, with 100% sensitivity and 63% specificity. The AUC for the absolute lymphocyte count was 0.17 (p-value less than 0.001), indicating a poor predictive ability. The optimal cutoff point for the absolute lymphocyte count was 2.35, with 40% sensitivity and 97% specificity. The AUC for the neutrophil-to-lymphocyte ratio was 1 (p-value less than 0.001), indicating a perfect predictive ability. The optimal cutoff point for the neutrophil-to-lymphocyte ratio was 0.95, with 100% sensitivity and 91% specificity. The AUC for the platelet-to-lymphocyte ratio was 0.58 (p=0.041), indicating a fair predictive ability. The optimal cutoff point for the platelet-to-lymphocyte ratio was 88.5, with 79% sensitivity and 97% specificity.

Table 7. ROC Analysis for Prediction of Asthma Exacerbation

PARAMETER	AUC	P-VALUE	CUTOFF POINT	SENSITIVITY	SPECIFICITY
ABSOLUTE NEUTROPHIL COUNT (10^9/L)	1	< 0.001*	2.65	100 %	63 %
ABSOLUTE LYMPHOCYTE COUNT (10^9/L)	0.17	< 0.001*	2.35	40%	97 %
NEUTROPHIL-TO-LYMPHOCYTE RATIO	1	< 0.001*	0.95	100%	91 %
PLATELET-TO-LYMPHOCYTE RATIO	0.58	.041	88.5	79 %	97 %

*p-value is significant, AUC: Area Under the Curve

4. Discussion

A statistically insignificant distinction regarding age and sex has been observed between the two investigated groups.

Consistent with our findings, Pan R et al.[9] aimed to assess the correlations of NLR, NAR, and NBR with the diagnosis of childhood asthma to ascertain their potential utility in clinical diagnosis. This retrospective case-control investigation included 89 asthmatic kids and 53 healthy kids from the Wuxi Children's Hospital, affiliated with Nanjing Medical University. They reported that statistically insignificant distinction has been observed among the study groups regarding age and sex.

The cases group had a significantly higher mean white blood cell count than the control group (10.61±3.37 versus 6.82±1.5, p-value less than 0.001). Similarly, the cases group had a significantly higher absolute neutrophil count (7±1.7 versus 2.69±1.5, p-value less than 0.001) and a significantly lower absolute lymphocyte count (2.24±0.48 versus 27±0.24, p-value less than 0.001) than the control group. The cases group also had a significantly higher platelet count (296.63±67.88 versus 300.17±49.93, p-value less than 0.001) and a significantly higher C-reactive protein level (6.87±1.9 versus 1.87±0.58, p-value less than 0.001) than the

control group. Nevertheless, insignificant distinctions have been observed between the two groups regarding hemoglobin, total protein, and albumin levels. The cases group had a significantly higher neutrophil-to-lymphocyte ratio (3.45±1.75 versus 1±0.13, p-value less than 0.001) and platelet-to-lymphocyte ratio (126.81±43.76 versus 110.58±10.14, p-value less than 0.001) than the control group.

Our outcomes were consistent with Zhu X, et al.,[10] who found that, regarding the laboratory data, levels of CRP, NLR, WBC, and PLR were elevated in the asthma group than the control group (p-value less than 0.001 for CRP, NLR and WBC; p-value equals 0.031 for PLR). The asthma group had significantly reduced absolute lymphocyte counts and PLT levels compared to the control group (p-value less than 0.001, p-value equals 0.013, respectively). Insignificant distinctions have been observed among the asthmatic group and the control group regarding hemoglobin and total protein levels (p-value equals 0.967 and p-value equals 0.714, respectively).

In our study, we found that the cases group had a significantly lower mean FEV1 (71.67±8.37) than the control group (78.84±1.52, p-value less than 0.001). Similarly, the cases group had a significantly lower mean FEV1/FVC ratio (86.15±13.85) than the control group (95±0.00, p-value less than 0.001).

Our outcomes were consistent with Snijders et al.,[11] who aimed to investigate cell counts and inflammatory mediators (ECP, eotaxin, IL-8, and TNFα) in a group of asthmatic kids versus non-atopic, non-asthmatic kids. They reported that the cases group had a significantly lower mean FEV1 (90±2) than the control group (102 ± 2, p-value less than 0.001). Similarly, the cases group had a significantly lower mean FEV1/FVC ratio (91 ± 2) than the control group (94 ± 2, p-value less than 0.001).

In our study, we found that according to the PRAM score, 63 (63%) were classified as mild, 20 (20%) as moderate, and 17 (17%) as severe.

Our outcomes were consistent with Zhu X, et al.,[10] who found that a total of 86 kids with exacerbated asthma were divided into 54(62.7%) had mild, 17(20%) had moderate, and 15(17%) had exacerbation of asthma.

The comparison between the mild, moderate, and severe groups within the case group and the control group. We found that the severe group had a notably higher mean age, significantly different from the other groups. This group also showed elevated mean WBC count and ANC, both with a significant distinction, suggesting a more active immune response. Interestingly, the moderate group recorded the highest mean ALC, with this distinction being statistically significant. The severe group continued to demonstrate higher mean values in Total Protein and Albumin levels, both showing significant distinctions. The control group exhibited the highest mean Platelet Count, with this distinction being statistically significant. In contrast, the mild group had a notably high mean C-reactive Protein Level, again with a significant distinction from the other groups. Further, the severe group showed the highest mean values for the NLR and PLR, both with significant distinctions. However, the mild group displayed the best mean pulmonary function, as indicated by the highest FEV1 value, though the p-value for this comparison was not specified.

Our outcomes were consistent with Zhu X, et al., [10], who stated that the comparison between the mild, moderate, and severe groups, in the severe group, had elevated mean WBC count and ANC, both with a significant distinction, suggesting a more active immune response. Interestingly, the moderate group recorded the highest mean ALC, with this distinction being statistically significant. The severe group continued to demonstrate higher mean values in Total Protein and Albumin levels, both showing significant distinctions. Further, the severe group showed the highest mean values for the NLR and PLR, both with significant distinctions.

In our study, we found that the AUC for the absolute neutrophil count was 1 (p-value less than 0.001), indicating a perfect predictive ability. The optimal cutoff point for the absolute neutrophil count was 2.65, with 100% sensitivity and 63% specificity. The AUC for the absolute lymphocyte count was 0.17 (p-value less than 0.001), indicating a poor predictive ability. The optimal cutoff point for the absolute lymphocyte count was 2.35, with 40% sensitivity and 97% specificity. The AUC for the neutrophil-to-lymphocyte ratio was 1 (p-value less than 0.001), indicating a perfect predictive ability. The optimal cutoff point for the neutrophil-to-lymphocyte ratio was 0.95, with 100% sensitivity and 91% specificity. The AUC for the platelet-to-lymphocyte ratio was 0.58 (p=0.041), indicating a fair predictive ability. The optimal cutoff point for the platelet-to-lymphocyte ratio was 88.5, with 79% sensitivity and 97%specificity.

Wawryk-Gawda E, et al., [12] who found that a receiver operating characteristic curve (ROC) of analysis of results of asthma cases and control; the proposed cut-off point of NRL was 0.53, area under the ROC curve (AUC) = 0.614, positive predictive value (PPV) = 0.81, negative predictive value (NPV) = 0.49, and accuracy (ACC) = 0.76.

4. Conclusion

We demonstrated that neutrophil to lymphocyte ratio and platelet to lymphocyte ratio substantially elevated throughout acute exacerbations of asthma in kids. The results indicate that these characteristics may serve as markers for acute exacerbation cases of childhood asthma. These low-cost, easily administered, and widely accessible tests might be highly beneficial in pediatric asthma management.

Disclosure

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Authorship

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