

# The Clinical Significance of Complete Blood Count Parameters for Frequent Emergency Department Admissions and Re-hospitalisation in Patients with Asthma Attacks Requiring Hospitalisation

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## ABSTRACT

**Objective:** The aim of this study was to investigate factors associated with emergency department (ED) admission and re-hospitalization within 1 year following a baseline asthma attack requiring hospitalization, and to investigate the role of complete blood count (CBC) parameters in these attacks.

**Methods:** This was a retrospective, observational study of patients hospitalized due to an asthma attack between September 2015 and September 2017. The number of ED admissions and re-hospitalizations due to an asthma attack within a year of the original admission was investigated and predictive factors related to frequent ED admissions ( $\geq 2$ ) and re-hospitalization were analyzed.

**Results:** Among the 59 study patients, the mean age was  $58 \pm 16$  years and 9 (15%) were male. Follow-up data revealed that 15 (25%) patients had frequent ED admissions and 20 (34%) patients were re-hospitalized within a year. Demographic details, additional diseases, and the baseline C-reactive protein level were not found to be predictive of subsequent asthma attacks. A baseline higher count of leukocytes ( $p=0.003$ ) and neutrophils ( $p=0.001$ ) and the ratio of neutrophils to lymphocytes (NLR) ( $p=0.017$ ) were found to be statistically significant in patients with frequent ED admissions. The risk of re-hospitalization was found to increase with a higher baseline NLR ( $p=0.022$ ) and platelet-to-lymphocyte ratio (PLR) ( $p=0.024$ ).

**Conclusion:** CBC analysis can provide important clues for prognosis in asthma attacks. The NLR should be considered as a possible indicator of frequent ED admissions, and the NLR and PLR should be taken into account as potential signs of re-hospitalization.

## INTRODUCTION

Asthma attacks are conditions which require urgent intervention, cause significant morbidity and might be life-threatening. The attacks are the most common cause of emergency department admissions and constitute an important part of the expenditures related to asthma.<sup>[1]</sup> Despite the current medical treatments, there has been no significant decrease in emergency admissions.<sup>[2,3]</sup>

The number of emergency department admissions and hospitalizations are important determinants for the

severity of asthma and attack which might be mortal. Some asthma patients have frequent attacks and it could not have been verified clearly which factors are associated with frequent attacks. It has been reported that the factors such as age<sup>[4,5,6]</sup>, non-white race<sup>[4,6]</sup>, low socioeconomic level<sup>[7]</sup>, female gender<sup>[5,6]</sup>, psychopathological status, chronic sinusitis, gastroesophageal reflux disease, obstructive sleep apnea syndrome<sup>[8]</sup> are associated with frequent attacks. Nevertheless, there are also studies that have not determined the relationship between the age<sup>[7,9]</sup> and gender<sup>[4,7,9]</sup> and the attacks.

In recent years, the effect of whole blood count parameters on the severity and progression of chronic diseases has been questioned. The ratio of neutrophils to lymphocytes (NLR) as an indicator of inflammation has been found to be associated with the severity of the disease and hospitalizations in chronic obstructive pulmonary disease,<sup>[10]</sup> diabetes mellitus and hypertension.<sup>[10,11]</sup> For the association of asthma with whole blood count parameters, there are few studies conducted with different patient groups and different methods. In uncontrolled asthma patients, the ratio of eosinophils to lymphocytes (ELR), eosinophils to neutrophils (ENR) and NLR values were found to be high in eosinophilic phenotype.<sup>[12]</sup> In children with asthma, NLR has been associated with hospitalization and attacks.<sup>[13,14]</sup> The results of the study investigating the relationship between the number of episodes and NLR values in adult asthma show some differences.<sup>[9,15]</sup>

The aim of this study was to investigate the factors associated with asthma attacks requiring emergency admissions and re-hospitalization in a year following asthma attacks requiring hospitalization and to investigate the relationship between NLR and other blood count parameters and the attacks.

## MATERIALS AND METHODS

This is a single-center, retrospective observational study conducted in a pulmonology clinic of a secondary state hospital.

From the hospital automation system between September 2015 and September 2017, the medical files of 131 patients which were hospitalized with the diagnosis of asthma [ICD-10 (10<sup>th</sup> revision of the international classification of diseases): J45, J45.0, J45.1, J45.8, J45.9 codes] were evaluated.

### Inclusion criteria:

- The patients whose asthma diagnosis has been confirmed by a pulmonologist<sup>[16]</sup>
- The patients who have asthma as a hospitalization reason
- The patients with one-year follow-up in our hospital

### Exclusion criteria:

- Hospitalizations not caused by asthma attacks (diagnoses such as pneumonia, malignancy, interstitial lung failure, decompensated heart failure, restrictive lung failure, pulmonary embolism)
- Patients who do not continue clinical follow-up in our hospital

Patients with recurrent hospitalizations were enrolled once with their first hospitalization. 59 patients hospitalized with asthma attack and followed up in our clinic were included in the study (Fig. 1). One-year follow-up of the patients after the attack was investigated.

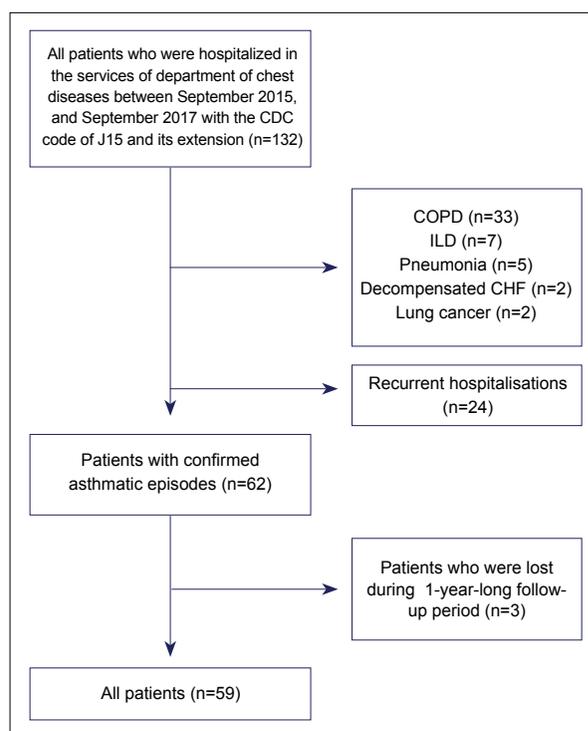


Figure 1. Patient selection flow chart.

### Recorded data

Demographic characteristics, comorbidities, basal whole blood count parameters including leukocyte ( $10^3/L$ ), neutrophil ( $10^3/L$ ), lymphocyte ( $10^3/L$ ), platelet ( $10^3/L$ ), eosinophil ( $10^3/L$ ), eosinophil (%), hemoglobin (g/dl) and C-reactive protein (CRP) (mg/l) values, PA chest radiographs and other investigations were performed. All hospital admissions from the automation system were examined and additional diseases were re-investigated. Hospitalization periods were recorded. Pulmonology outpatient clinic and asthma-related emergency department admissions of all patients were reviewed within 12 months from the date of discharge and re-hospitalization requirements were investigated. Treatment results and hospitalization requirements were recorded from all emergency admissions. The ratio of neutrophils to lymphocytes (NLR), the ratio of platelets to lymphocytes (PLR), the ratio of eosinophils to lymphocytes (ELR), the ratio of eosinophils to neutrophils (ENR) were calculated.

### Study design

All patients were divided into 2 groups, according to the number of emergency admissions as less than 2 emergency department admissions and  $\geq 2$  emergency admissions. And the factors associated with frequent emergency visits were investigated.

### Statistical analysis

The data were expressed as mean $\pm$ standard deviation. The parameters associated with frequent emergency de-

partment admissions were calculated by student's t-test and chi-square methods. The factors associated with re-hospitalization within a year were investigated by Cox regression analysis. The data were recorded in SPSS (SPSS for Windows, version 16.0; SPSS Inc.; Chicago, IL, USA) 16.0 statistics program. The values were calculated in 95% confidence interval and p value <0.05 was considered as significant.

## RESULTS

The mean age of the patients included in the study was  $58 \pm 16$  years and 9 (15%) of them were male. Forty-six (78%) patients had at least one comorbidity. The most commonly recorded diseases were hypertension (39%), anxiety disorder or depression (27%) and diabetes mellitus (24%). The mean hospital stay was  $6 \pm 3.4$  (1-19) days.

In the follow-up of the patients, the mean number of outpatient admissions was  $2.8 \pm 2.1$  (0-8),  $1.1 \pm 1.7$  (0-8), and hospitalization  $0.5 \pm 1$  (0-4) within one year. While twenty-nine (49%) patients never applied to the emergency department, 15 (25%) patients admitted once. Other patients were admitted to the emergency department 2-8 times. When the factors associated with frequent ( $\geq 2$ ) emergency admissions were investigated; there was no

statistically significant relationship between demographic features and comorbidities ( $p > 0.05$ ). Basal leukocyte ( $p = 0.003$ ) and basal neutrophil ( $p = 0.001$ ) values were higher in patients with frequent emergency visits. There was no significant relationship between CRP, hemoglobin and eosinophil values ( $p > 0.05$ ). PLR, ELR and ENR values of hematological parameters were not correlated with the frequency of attacks; higher NLR ( $p = 0.017$ ) values were found in patients with frequent emergency visits (Table 1).

Following the first hospitalization, re-hospitalization was recorded in 20 (34%) patients. The hospitalizations occurred after a median of  $9 \pm 1.4$  months. There was no correlation between demographic characteristics and comorbidities and re-hospitalization ( $p > 0.05$ ). Leukocyte, eosinophil, thrombocyte hemoglobin values of whole blood count parameters were not associated with re-hospitalizations ( $p > 0.05$ ). High NLR ( $p = 0.022$ ) and high PLR ( $p = 0.024$ ) values increased the risk of attacks requiring re-hospitalization (Table 2).

## DISCUSSION

When the morbidity, labor loss and high health expenditures caused by asthma attacks are considered, it is important to identify the risk group. In our study, the relation-

**Table 1.** Factors associated with frequent emergency admission after asthma attack

	Total n=59 (n=44)	<2 emergency admissions (n=15)	$\geq 2$ emergency admissions	p
Gender				
Male	9 (15)	7 (16)	2 (13)	0.999
Female	50 (85)	37 (84)	13 (87)	
Age	$58 \pm 16$ (20-88)	$58 \pm 16$	$58 \pm 14$	0.903
Any comorbidities	46 (78)	33 (75)	13 (87)	0.482
Hypertension	23 (39)	17 (39)	6 (40)	1.000
Anxiety/depression	16 (27)	12 (27)	3 (20)	0.738
Diabetes Mellitus	14 (24)	10 (23)	4 (27)	0.736
Cardiac disease	8 (14)	6 (14)	2 (13)	1.000
Thyroid disease	5 (9)	3 (7)	2 (13)	0.593
Allergic rhinitis	7 (12)	6 (14)	1 (7)	0.666
Gastroesophageal reflux	5 (9)	4 (9)	1 (7)	1.000
Leukocyte ( $10^3/L$ )	$9.7 \pm 4.1$	$8.8 \pm 3.3$	$12.4 \pm 5.1$	0.003
Eosinophil (%)	$2.1 \pm 3.3$ (0-16)	$2.0 \pm 3.3$	$2.4 \pm 3.3$	0.750
Neutrophil ( $10^3/L$ )	$6.9 \pm 3.6$ (1.4-20.3)	$6.0 \pm 2.7$	$9.4 \pm 4.7$	0.001
Lymphocyte ( $10^3/L$ )	$2.4 \pm 3.1$ (0.4-22.5)	$2.6 \pm 3.6$	$1.9 \pm 1.2$	0.502
Thrombocyte ( $10^3/L$ )	$266 \pm 78$ (99-465)	$253 \pm 66$	$304 \pm 98$	0.058
CRP (mg/L)	$41.7 \pm 58.7$	$36.8 \pm 47$	$55 \pm 83$	0.307
Hemoglobin (g/dL)	$12.7 \pm 1.6$	$12.6 \pm 1.7$	$12.9 \pm 1.5$	0.598
NLR	$5.1 \pm 4.8$	$4.2 \pm 3.5$	$7.6 \pm 7.1$	0.017
PLR	$189 \pm 146$	$175 \pm 130$	$229 \pm 185$	0.225
ELR	$0.09 \pm 0.15$	$0.09 \pm 0.17$	$0.08 \pm 0.09$	0.796
ENR	$0.03 \pm 0.06$	$0.03 \pm 0.05$	$0.05 \pm 0.07$	0.537
Length of stay in hospital (day)	$6.0 \pm 3.4$	$5.9 \pm 3.6$	$6.4 \pm 3.0$	0.666

**Table 2.** Factors associated with the risk of exacerbation requiring hospitalization within one year after an asthma attack

	HR	CI (95%)	P
Gender	0.990	0.963-1.018	0.477
Age	0.630	0.210-1.889	0.432
Length of stay in hospital (day)	1.019	0.906-1.146	0.758
Hypertension	0.903	0.369-2.210	0.824
Anxiety/depression	0.983	0.357-2.705	0.974
Diabetes mellitus	1.253	0.419-3.749	0.680
Cardiac disease	0.427	0.155-1.177	0.128
Thyroid disease	0.861	0.200-3.710	0.843
Allergic rhinitis	3.018	0.404-5.579	0.201
Gastroesophageal reflux	1.817	0.243-13.665	0.523
Leukocyte (10 <sup>3</sup> /L)	1.083	0.970-1.209	0.172
Eosinophil (%)	1.056	0.939-1.188	0.397
Neutrophil (10 <sup>3</sup> /L)	1.099	0.950-1.233	0.242
Lymphocyte (10 <sup>3</sup> /L)	0.661	0.399-1.094	0.038
Thrombocyte (10 <sup>3</sup> /L)	1.004	0.997-1.008	0.192
CRP (mg/L)	1.004	0.997-1.012	0.313
Hemoglobin (g/dL)	0.999	0.760-1.313	0.993
NLR	1.090	1.020-1.165	0.022
PLR	1.003	1.001-1.005	0.024
ELR	2.833	0.284-28.306	0.418
ENR	20.804	0.489-84.161	0.125

CRP: C-reactive protein; ELR: Erythrocytes to lymphocytes ratio; ENR: Erythrocytes to neutrophils ratio; NLR: Neutrophils to lymphocytes ratio; PLR: Platelets to lymphocytes ratio.

ship between adult asthma attacks and the risk of relapses was examined and important results were obtained regarding complete blood count parameters. High NLR values in episodes requiring hospitalization were determined to be a risk indicator for frequent emergency admissions and re-hospitalization in the following year. Furthermore, the relationship between high PLR values and re-hospitalization was demonstrated for the first time.

The rates of hospital admissions, exacerbations and hospitalizations in asthma patients vary widely in relation to the clinical setting, study group and study method. Griswold et al. evaluated 3000 emergency admissions due to asthma attacks in the United States. In the previous year, 73% of these patients reported at least one more and 21% had more than five emergency admissions.<sup>[4]</sup> The number of hospitalizations with asthma exacerbation was  $2.1 \pm 2.3$  and the number of emergency admissions was  $4.2 \pm 4.1$  in one year.<sup>[17]</sup> In another study, it was analyzed that 70% of uncontrolled asthma patients required outpatient visits and 36% of them required emergency visits in one year and 14% of these patients required hospitalization. In asthma patients under control, these rates were found to be 43%, 10% and 3%, respectively.<sup>[18]</sup> Adams et al. reported that in the first year following hospitalization due to attacks,  $\geq 2$  emergency admissions were found in 11%

and re-hospitalizations in 13%.<sup>[19]</sup> In our study, less than half of the patients admitted to the emergency room after the attack and more than one third of the patients were hospitalized again.

Emre et al. reported that the average hospitalization day due to asthma attack was  $8.5 \pm 4.6$  days in the Pulmonology Clinics of a state hospital in Manisa.<sup>[20]</sup> In our study, the mean length of stay was two days shorter. It has been reported that meteorological changes might be associated with the attacks.<sup>[21]</sup> We believe that different hospitalization times may be associated with meteorological changes and further studies are needed on the factors affecting the attack severity and duration.

Different results have been presented regarding the factors affecting the frequency of attacks. Age<sup>[4,5,6,8]</sup> and female gender<sup>[5]</sup> have been reported as risk factors for frequent attacks. In addition to studies reporting that the sex and frequency of attacks were unrelated<sup>[4,6]</sup>; Eisner et al.<sup>[7,9]</sup> reported that there was no relationship between demographic features and frequency of attacks and similarly in their study, no relationship was found between age and gender and frequency of attacks. In asthma exacerbations, the relationship between psychopathological status and chronic sinusitis has been demonstrated for the frequency of exacerbations which was recorded in the previous year<sup>[8]</sup> In our study, no association of comorbidities with attacks was found. We think that the association of comorbidities and demographic characteristics with the frequency of attacks should be investigated in studies with larger sample size.

In recent years, the use of whole blood count parameters as an indicator of inflammation in asthma has been questioned. Studies with different methods and different patient groups have been published. High NLR values have been reported to increase the risk of asthma attacks for all age groups.<sup>[9,14]</sup> Gungen et al. have compared stable asthma patients with healthy control group. In asthma, NLR values were found to be higher and it increased when the disease was not under control, and the number of attacks and NLR values were found to be unrelated.<sup>[15]</sup> In the pediatric patient group, higher NLR values than in healthy volunteers have been reported, while hospitalization and NLR have been reported unrelated.<sup>[13]</sup> Zhang et al. have found that peripheral blood ELR, ENR and NLR values were correlated among asthma phenotypes in asthmatic patients receiving treatment but not under control.<sup>[12]</sup> In our study, ELR and ENR values were not correlated with the number of attacks and hospitalizations. However, NLR values were higher in patients with frequent emergency admissions and those who needed re-hospitalization.

The neutrophils are thought to play a key role in triggering and resolving an asthma attack.<sup>[22]</sup> Neutrophils have been shown to cause airway constriction in severe asthma rather than stable asthma.<sup>[23,24]</sup> The lymphocytes are reduced in acute stress conditions such as myocardial infarction.<sup>[25]</sup> NLR was thought to be more accurate than neutrophil or lymphocyte analysis alone.<sup>[26]</sup> Our results suggest that high

NLR is associated with both frequent emergency admissions and re-hospitalization. The neutrophils alone were also associated with frequent emergency admissions.

The platelets have been shown to play important roles in immune system regulation and inflammation. Triggering factors stimulate the release of inflammatory cytokines and stimulate white blood cells.<sup>[27,28]</sup> It has been shown that platelets are activated in asthma and CD154 expression is increased.<sup>[29,30]</sup> CD154 release has been shown to activate platelets during allergen sensitization in asthma, stimulating other white blood cells to cause inflammation to become more pronounced.<sup>[31]</sup> In the literature, we could not find a study investigating the relationship between asthma attacks and platelet count and PLR. In our study, the platelets were not associated with frequent emergency admissions, whereas high PLR values were associated with severe episodes requiring hospitalization.

The most important limitation of this study was that it was retrospective and uni-centered and the physiological parameters of the patients were not recorded. As a retrospective study, educational status, treatment protocols and treatment compliance of the patients could not be examined. However, all patients were followed up by the pulmonologists at our center. The fact that all district hospitals are connected to the same automation system has ensured that comorbidities and hospital admissions were reliably detected.

## CONCLUSION

In conclusion, rapid, simple and easily accessible complete blood count analysis in asthma attacks can provide important clues for the prognosis of the patients. For frequent emergency admissions, NLR values and for the attacks which require re-hospitalization, NLR and PLR values should be considered as an indicator of inflammation.

### Ethics Committee Approval

Ethics committee approval with the number 2011-KAEK-27/2018-1800156929 was received for the study.

### Informed Consent

Informed consent was not obtained due to the retrospective nature of the study.

### Peer-review

Internally peer-reviewed.

### Authorship Contributions

Concept: F.T.A., M.E.O., A.T., H.T., G.S., M.A., T.S.; Design: F.T.A., M.E.O., A.T., H.T., G.S., M.A., T.S.; Supervision: F.T.A., M.E.O., A.T., H.T., G.S., M.A., T.S.; Fundings: F.T.A., M.E.O., A.T.; Materials: F.T.A., M.E.O., A.T., H.T., G.S.; Data: F.T.A., M.E.O., A.T., H.T., G.S.; Analysis: F.T.A., M.A.; Literature search: F.T.A., T.S.; Writing: F.T.A., M.A., T.S.; Critical revision: F.T.A., T.S.

### Conflict of Interest

None declared.

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## Hastane Yatışı Gereken Erişkin Astım Ataklarında Tam Kan Sayımı Parametrelerinin Sık Acil Başvuruları ve Yeniden Hastane Yatışı İçin Prognostik Önemi

**Amaç:** Bu çalışmanın amacı, hastane yatışı gerektiren astım ataklarını takiben, bir yıl içinde yeniden acil başvuruları ve hastane yatışı ile ilişkili faktörleri araştırmak, tam kan sayımı parametrelerinin ataklar ile ilişkisini incelemektir.

**Gereç ve Yöntem:** Çalışma, retrospektif gözlemsel bir çalışma olup Eylül 2015-Eylül 2017 arasında kliniğimizde astım atağı nedeniyle yatırılan hastalar değerlendirildi. Hastaların demografik özellikleri, ek hastalıkları ve bazal kan sayımı parametreleri kaydedildi. Takip eden bir yıl içinde sık acil başvuruları ( $\geq 2$ ) ve yeniden hastane yatışı ile ilişkili faktörler analiz edildi.

**Bulgular:** Çalışmaya alınan 59 hastanın yaş ortalaması  $58 \pm 16$  idi, 9 hasta (%15) erkekti. Bir yıl içinde 15 (%25) hastada sık acil başvurusu, 20 (%34) hastada yeniden hastane yatışı kaydedildi. Demografik özellikler, ek hastalıklar ve bazal C-reaktif protein değerleri ile daha sonraki ataklar arasında ilişki saptanmadı ( $p > 0.05$ ). Sık acil başvurusu olan hastalarda bazal lökosit ( $p = 0.003$ ), nötrofil ( $p = 0.001$ ) ve nötrofillerin lenfositlere oranı (NLO) ( $p = 0.017$ ) istatistiksel olarak anlamlı yüksekti. Yeniden hastane yatışının ise yüksek bazal NLO ( $p = 0.022$ ) ve PLO ( $p = 0.024$ ) değerleri ile ilişkili olduğu belirlendi.

**Sonuç:** Tam kan sayımı analizi astım ataklarında prognoz için önemli ipuçları sağlayabilir. Sık acil başvuruları riski için NLO; yeniden yatış gerekecek ataklar için ise NLO ve PLO değerleri dikkate alınmalıdır.

**Anahtar Sözcükler:** Astım; eozinofil; lenfosit; nötrofil.