doi • 10.5578/tt.27626
Tuberk Toraks 2017;65(1):25-31
Geliş Tarihi/Received: 21.01.2016 • Kabul Ediliş Tarihi/Accepted: 31.03.2017

KLİNİK ÇALIŞMA
RESEARCH ARTICLE

Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease

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SUMMARY

Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease

Introduction: *The prognostic significance of neutrophil-to-lymphocyte ratio (NLR), derived-neutrophil-to-lymphocyte ratio (d-NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) have been shown in many diseases. To the best of our knowledge, there is no published report evaluation of those parameters in acute exacerbation of chronic obstructive pulmonary disease (AECOPD). The aims of this study are to evaluate the parameters in predicting in-hospital mortality in patients with AECOPD.*

Materials and Methods: *This is a retrospective study in two referral hospitals in Tabriz and Urmia, Iran. NLRs, PLR, LMR, and d-NLR were calculated from the admission day complete blood count of patients with AECOPD. Comparison was made between patients who died in hospital and those discharged alive.*

Results: *Of 315 patients, 70 (22.2%) died in the hospital and 245 (77.8%) were discharged alive. The mortality rate was higher in patients with NLR ≥ 4 than with NLR < 4 (24% vs. 9.5% p value < 0.001). Multivariate analysis revealed NLR (p= 0.001) were independently associated with in-hospital mortality. NLR had the highest odds ratio for death both in univariate (OR= 3.80) and multivariate (OR= 3.50) analyses. The area under the receiver-operating characteristic curve for NLR in predicting in-hospital death was 0.72 (95% CI: 0.62-0.81; p< 0.001). PLR and LMR did not show significant relation to in-hospital death in AECOPD.*

Conclusion: *This study shows for the first time that higher NLR is positively associated with in-hospital mortality in AECOPD.*

Key words: *Chronic obstructive pulmonary disease, hospital mortality, acute exacerbation chronic obstructive pulmonary disease, neutrophil-lymphocyte ratio, platelet-to-lymphocyte ratio*

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ÖZET

Kronik obstrüktif akciğer hastalığı alevlenme olgularında başvuru nötrofil lenfosit oranı ile prognoz arasındaki ilişki

Giriş: *Nötrofil lenfosit (NLO), hesaplanmış nötrofil lenfosit (h-NLO), platelet lenfosit (PLO) ve lenfosit monosit (LMO) oranlarının çeşitli hastalıklarda prognoz tahmininde önemli olduğu gösterilmiştir. Bildiğimiz kadarı ile bu oranların kronik obstrüktif akciğer hastalığı (KOAH) alevlenmesi olgularında incelendiği çalışma bulunmamaktadır. Bu çalışmanın amacı bu parametrelerin KOAH alevlenme nedeni ile hastanede yatan olguların hastane yatış mortalitesini tahminindeki faydasını araştırmaktır.*

Hastalar ve Metod: *Bu çalışma İran'daki Tebriz ve Urmia şehirlerindeki iki hastanede yapılan retrospektif bir çalışmadır. KOAH alevlenme tanılı olguları başvuru hemogram sonuçlarından NLO, PLO, LMO ve h-NLO hesaplandı. Hastanede yatarken ölen ve şifa ile taburcu olan olguların sonuçları karşılaştırıldı.*

Bulgular: *Toplam 315 olgunun 70 (%22.2)'i hastanede öldü. Kalan 245 (%77.8) olgu şifa ile taburcu edildi. NLO ≥ 4 olanlarda NLO < 4 olanlara göre mortalite daha yüksekti (%24'e karşın %9.5 p< 0.001). Multivariate analizlere göre NLO (p= 0.001) hastane mortalitesinin bağımsız göstergelerinden birisiydi. NLO hem univariate (OR= 3.80) hem multivariate (OR= 3.50) analizlerde en yüksek odds ratioya (OR) sahipti. NLO için eğri altında kalan alan (ROC) 0.72 (%95 CI: 0.62-0.81; p< 0.001) idi. PLO ve LMO ile hastane mortalitesi arasında istatistiksel anlamlı ilişki saptanmadı.*

Sonuç: *İlk kez bu çalışmada KOAH alevlenme ile başvuran hastalarda hastane mortalitesi ile NLO arasında istatistiksel anlamlı ilişki olduğu gösterildi.*

Anahtar kelimeler: *Kronik obstrüktif akciğer hastalığı, hastanede yatış mortalitesi, KOAH alevlenme, nötrofil lenfosit oranı, platelet lenfosit oranı*

INTRODUCTION

The World health organization (WHO) in fact sheet number 315 (March 2015) stated that: "Chronic obstructive pulmonary disease (COPD) is a life-threatening lung disease that interferes with normal breathing. It is more than a "smoker's cough". More than 3 million people died of COPD in 2012, which is equal to 6% of all deaths globally that year. More than 90% of COPD deaths occur in low- and middle-income countries." (1).

COPD was ranked as the sixth cause of death in 1990, will become the third leading cause of death worldwide by 2020. Acute exacerbations of COPD (AECOPD) are the most common causes of hospitalization and death among COPD patients (2). Different biochemical markers have been used in AECOPD patients to predict the outcome; however, many of them are time consuming with extra cost.

It has been well recognized that inflammation plays an important role in COPD. Therefore, circulating biomarkers that reflect the status of inflammation can serve as potential predictors for the prognosis of AECOPD patients.

In recent years, peripheral blood neutrophil-to-lymphocyte ratio (NLR), derived-neutrophil-to-lymphocyte ratio (d-NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) are widely investigated as useful predictors for prognosis in many disease (3).

NLR is a predictor of mortality in several diseases (4). Elevated NLR was an independent prognostic factor for chronic kidney disease, diabetes mellitus, coronary artery disease, appendicitis, systemic lupus erythematosus, Sjogren syndrome, and cystic fibrosis (5-12). In several other diseases, an elevated NLR has been implicated as the marker of a poorer outcome. In patients with stage 4 chronic kidney disease, those with an NLR > 3 had a worse prognosis and a significantly faster progression to the dialysis (5).

However, to the best of our knowledge, only one study in COPD patients, by Gunny et al., showed that in AECOP patients NLR was higher than in stable COPD, and in stable COPD higher than in control. They haven't studied the relation to outcome (13). LMR, d-NLR, and PLR have not been studied in COPD so far.

The aim of this study was to detect a relationship between simple, inexpensive, and easily available NLR, d-NLR-PLR, and LMR parameters with outcome in AECOPD.

MATERIALS and METHODS

This is a retrospective study of patients who were hospitalized with AECOPD in two referral centers in the cities of Tabriz (Imam-Reza hospital) and Urmia (Imam-Khomeini hospital), Iran, from July 2012-2015. Hospital charts were reviewed for admission day CBC parameters (Hematology cell counter Technikon H1, USA). Patients with coexistent hematologic or malignant disorders or those patients with discharge on own consent, were excluded.

Statistical Analysis

We used SPSS 23 IBM software for analysis. We grouped patients with AECOPD to two groups, those who died in hospital and those who discharged hospital alive. We have made comparison of two groups, and $p< 0.05$ was considered statistically significant. The CBC parameters were entered to SPSS software. Then NLR, PLR, LMR, d-NLR were computed as new variables by SPSS "transform, compute" orders. NLR and PLR were calculated as the ratio of the neutrophils and platelets to lymphocytes, and LMR from lymphocytes to monocytes counts. d-NLR was calculated by dividing the absolute neutrophil count by the difference between leukocytes and neutrophil count [d-NLR= Neutrophil count to (white cell count-neutrophil count)].

Categorical data were described as frequencies and were compared using the chi-square test. To test the normal distribution, we used the Kolmogorov-Smirnov test. Differences in the continuous variables between groups were determined using Student's t-test or the Mann-Whitney U test for variables with or without normal distribution, respectively. Thereafter, we entered variables with significant association with mortality ($p< 0.05$) in univariate analysis to binary logistic regression analysis, with the "Enter" method. We used receiver-operating characteristic (ROC) curve analysis to identify the best discriminatory cut-off value for NLR, PLR, LMR, and d-NLR.

RESULTS

In total, 315 hospital charts were reviewed, and their demographic characteristics are presented in Table 1. Of 315 patients, 70 (22.2%) patients died in hospital and 245 (77.8%) left hospital alive. Tables 2 and 3 show univariate analysis and comparison of two groups of AECOPD (death in hospital and discharged alive) for categorical and continuous variables, respectively. NLR, d-NLR, anemia, thrombocytopenia, old age, and male sex had statistically significant association with in-hospital mortality. PLR, monocyte count, and presence of comorbidity were not statistically significant ($p> 0.05$). We used the binary logistic regression model to evaluate the values of age, sex, NLR, anemia, and thrombocytopenia as independent risk factors for in-hospital mortality. NLR showed the highest odds ratio, both in univariate analysis (Table 2, odds= 3.80), and in binary logistic regression analysis (Table 4, odds= 3.58).

In the ROC curve analysis, the NLR had the highest area under the curve (AUC) value of 0.717 (95% CI, 0.623-0.811) with a cut-off value of 4, and it had a sensitivity of 87%, specificity of 40%. Table 5 and Figure 1 show ROC curve results for NLR, LMR, PLR, neutrophils, and lymphocytes.

DISCUSSION

This study is the first to our knowledge that shows the association of NLR with mortality in patients with AECOPD. NLR was more predictive than neutrophil and lymphocyte counts alone because NLR integrates these two inflammatory markers, indicating opposing clinical outcomes. The suggested mechanisms for association of high NLR with poor outcome in cancers, is that a subpopulation of neutrophils suppresses T-cells activation through the production of reactive oxygen species, nitric oxide, and arginase (14,15). Assessment of the NLR gives information about two different immune pathways concomitantly, and is an indicator of the overall inflammatory status of the body. First, neutrophils that are responsible for lasting inflammation and second, the pathway that is related to lymphocytes, which have a regulatory function (16).

There are no similar studies in AECOPD; however,

Table 1. Demographic characteristics of patients

Variable	Discharged alive n (%)	Death in hospital n (%)	Total n (%)	p
Male	127 (73.0)	47 (27.0)	174 (55.2)	0.023
Female	118 (83.7)	23 (16.3)	141 (44.8)	
Age Mean ± SD	68.85 ± 10.90	73.54 ± 10.01	69.89 ± 10.87	0.001
Median	69	75	70	
Age ≥ 70 years	126 (82.9)	26 (17.1)	152 (48.3)	0.035
Age < 70 years	119 (73.0)	44 (27)	163 (51.7)	

Table 2. Univariate analysis of continues variables relation to in hospital death in AECOPD

	Discharge alive	Death	Total	p
Hb (mg/dL) Mean± SD	13.87 ± 2.58	12.41 ± 3.17	13.54 ± 2.79	0.00
Median	13.50	12.15	13.40	
WBC count/mm^3 Mean ± SD	8757 ± 3484	11411± 5911	9349 ± 4281	0.00
Median	8300	10150	8600	
Neutrophils count/mm^3 Mean ± SD	6921.92 ± 3342	9969 ± 5839	7599 ± 4217	0.00
Median	6280	8200	6500	
lymphocytes count/mm^3 Mean ± SD	1280 ± 815	931 ± 598	1203 ± 785	0.00
Median	1000	750	1000	
Monocytes count/mm^3 Mean ± SD	506 ± 310	618 ± 364	537 ± 328	0.06
Median	466	590	500	
Eosinophils count/mm^3 Mean ± SD	130.34 ± 142.14	58.95 ± 129	109.31 ± 141.97	0.00
Median	100.0	10.0	40.00	
Basophils count/mm^3 Mean ± SD	28.59 ± 54.41	15.41 ± 20.74	5.85 ± 5.68	0.126
Median	10	10	10	
NLR Mean ± SD	8.29 ± 7.56	17.00 ± 17.56	10.22 ± 11.19	0.00
Median	5.36	10.29	6.31	
LMR Mean ± SD	5.69 ± 25.38	1.77 ± 1.30	4.64 ± 21.75	0.00
Median	2.48	1.46	2.16	
D-NLR Mean ± SD	5.05 ± 4.23	8.67 ± 8.58	5.86 ± 5.68	0.00
Median	3.50	5.43	4.04	
Platelet Mean ± SD	186.478 ± 89.501	155.200 ± 87.497	179.505 ± 89.870	0.006
Median	181.000	147.500	175.500	
PLR Mean ± SD	2074 ± 192.4	241.38 ± 224.0	214.98 ± 200	0.15
Median	153.73	194.23	161	

Hb: Hemoglobin, WBC: White blood cells.

Table 3. Univariate analysis of nominal variables relation to in hospital death in AECOPD

Variable	Discharged alive n (%)	Death in hospital n (%)	Total n (%)	p	
NLR ≥ 4	150 (71.4)	60 (28.6)	210 (66.7)	0.000	3.80 (1.85-7.78)
NLR < 4	95 (90.5)	10 (9.5)	105 (33.3)		
No thrombocytopenia	166 (83.0)	34 (17.0)	200 (63.7)	0.003	2.25 (1.31-3.67)
Thrombocytopenia*	78 (68.2)	36 (31.6)	114 (36.3)		
Non-Anemic	174 (84.5)	32 (15.5)	206 (65.6)	0.000	2.95 (1.71-5.10)
Anemic†	70 (64.8)	38 (35.2)	108 (34.4)		
Comorbidity yes	160 (79.6)	41 (20.4)	201 (64.4)	0.246	NS
NO	82 (73.9)	29 (26.1)	111 (35.6)		

NS: Not significant, CI: Confidence interval, WBC: White blood cells, NLR: Neutrophils to lymphocytes ratio, d-NLR: Derived neutrophil to lymphocyte ratio, PLR: Platelet-to-Lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio.
* Thrombocytopenia: Platelet count < 15000/μL
† Anemia Hb > 12 in females and Hb < 13 in males (World Health Organization definition) (41).

these findings are consistent with several other studies in other inflammatory diseases. Elevated NLR associated with increased tumor necrosis factor (TNF) alpha, and interleukins of IL-6, IL-7, IL-8, IL-12, and IL-17 (17,18). These markers associated with poor outcome in critically ill patients. In patients with acute-on-chronic liver failure the NLR was an independent predictor for three-month mortality (19). Dirican et al., after studying 116 patients with sarcoidosis, reported that

Table 4. Binary logistic regression analysis of factors independently associated with in-hospital mortality of AECOPD patients

	B	p	Odds ratio (95%CI)
Anemia	1.172	0.000	3.230 (1.79-5.81)
NLR ≥ 4	1.277	0.001	3.586 (1.69-7.60)
Thrombocytopenia	0.665	0.027	1.944 (1.07-3.50)
Gender (Male)	0.475	0.135	1.608 (0.86-2.99)
Age ≥ 70	0.457	0.138	1.579 (0.86-2.89)
Constant	-0.555	0.088	

NLR: Neutrophils to lymphocytes ratio.

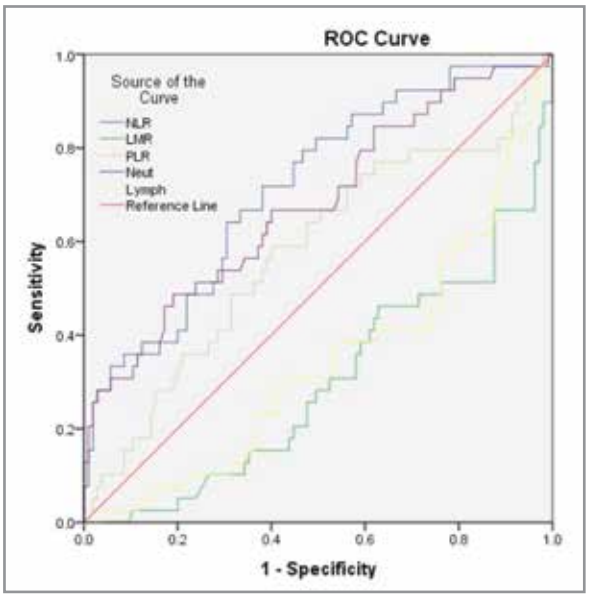

Figure 1. Receiver-operating characteristics (ROC) analysis of NLR, PLR, LMR, neutrophil, and lymphocytes to predict in-hospital mortality, and Table 5 cut-off values.

NLR increases with increasing stage of sarcoidosis (20). In a study by Aktimur et al. NLR value (> 9.9) was a diagnostic marker of acute mesenteric ischemia (21). Among the CBC components, only NLR was associated with gangrenous appendicitis (9). It has been suggested that elevated NLR has a better prognostic value than white blood cell count or C-reactive protein in acute appendicitis (22). In patients with acute atrial fibrillation successfully converted to sinus rhythm with amiodarone, those with high NLR had a higher rate of recurrence in the long-term follow up (23). Deng et al. with studying of 389 patients who had undergone gastrectomy, reported that preoperative NLR and d-NLR are prognostic biomarkers in patients with gastric cancer (24). The NLR has been used to predict outcomes in non-alcoholic fatty liver cystic fibrosis (12,25). NLR predicts long-term mortality in patients with ST-segment elevation myocardial infarction (26). A high pretreatment or preoperative NLR has been reported as an independent poor prognostic factor in cancers of lung, gastric breast, and colon (24,27-29). Tropan and co-workers showed in multivariate analysis an independent significant association between high NLR and poor outcome in 290 patients with diffuse large B-cell lymphoma (30).

In our study, there was a relation of mortality with d-NLR. This is expected and may have the same value and mechanism of NLR, there is no rational to calculate D-NLR. Only two studies have showed prognostic importance of d-NLR in colorectal cancer and gastric cancer (3,24). To the best of our knowledge, there is no study of d-NLR in non-cancer patients.

In our study, there was no association between PLR and mortality rate in the patients with AECOPD. This

Table 5. Area under curve and cut-off values for NLR, PLR, LMR, neutrophil and lymphocytes to predict in-hospital mortality, and Table 4 shows its results

Parameter	AUC	p	Cut of value	Sensitivity	Specificity
NLR	0.717 (0.623-0.811)	0.000	4	87%	40%
LMR	0.297 (0.200-0.394)	0.000	2	36%	41%
PLR	0.576 (0.465-0.686)	0.163	150	59%	46%
Neutrophilia	0.678 (0.576-0.781)	0.001	7700	51%	72%
Lymphopenia	0.340 (0.239-0.442)	0.003	1500	13%	69%

AUC: Area under curve, NLR: Neutrophils to lymphocytes ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio.

can be explained by the fact that both numerator (platelet count) and denominator (lymphocyte count) have changed in the similar direction, that is, decrement of both platelet and lymphocyte are associated with increased inpatient mortality rate. To the best of our knowledge, this is the first study of prognostic significance of PLR on the AECOPD patients. Platelets play an important role in inflammation. Thrombocytopenia is associated with poor outcome in AECOPD and several other diseases (31-35). Association of lymphopenia with mortality has already shown in sepsis, in critically ill emergency general surgical patients, and heart failure (36,37).

In our study, anemia also was associated with high mortality in AECOPD. Similar findings are reported in other studies (38).

In univariate analysis, LMR and lymphocyte count, but not monocyte count, showed significant association with mortality rate ($p< 0.05$); however, in multivariate analysis, LMR showed no association. This discrepancy is due to the higher impact of low lymphocyte count on the calculations, which is not affected significantly by the monocyte count.

Most reported studies about LMR are in malignant diseases, and there are rare studies in non-malignant diseases. Some studies showed association low LMR with tuberculosis (39,40). It is expected, monocytes are target cells for mycobacterial growth and lymphocytes are the major effectors for mycobacterial clearance (40).

The main limitation of our study is its retrospective nature; however, this limitation may be an advantage of a study that has no bias in management and discharge of patients.

CONCLUSION

Our results proved our hypothesis and indicated elevated NLR was a respective independent prognostic biomarker for in-hospital mortality in AECOPD. NLR was found to have a superior prognostic value with the highest sensitivity and specificity and the largest AUC, and the highest odds ratio for mortality in AECOPD. However LMR and PLR failed to show prognostic significance. We suggest the NLR, which is cheap and easily measurable even in the simplest health-care units, is practical to use for the follow-up of AECOPD.

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