Kocaeli Medical J 2017; 6; 2: 11-16

Koroner Arter Bypass Greft Hastalarında Pulmoner Fonksiyonlar ve Nötrofil Lenfosit Oranı Arasında Korelasyon Var mı?

Is There a Correlation Between Pulmonary Function Tests and Neutrophil Lymphocyte Ratio in Patients Undergoing Coronary Artery Bypass Grafting?

Serkan Tulgar[1], Olgar Bayserke[2], Onur Selvi[1], Zeliha Özer[1]
1Maltepe Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Ana Bilim Dalı, İstanbul, Türkiye
2Maltepe Üniversitesi Tıp Fakültesi, Kardiyovasküler Cerrahi Ana Bilim Dalı, İstanbul, Türkiye

ÖZ

GİRİŞ ve AMAÇ: *Pulmoner Fonksiyon Testleri (PFT) kardiyotorasik cerrahi öncesi preoperatif değerlendirmede sık başvurulan önemli bir testtir. Nötrofil lenfosit oranı ise birçok çalışmaya konu olmuş, bir çok hastalık ile ilişkisi olduğu ortaya konmuş bir biyomarkerdır. Benzer şekilde platellet lenfosit oranı (PLR) ve sistemik immun inflamatuar indexte çalışmalara konu olmaktadır. Bu çalışmada amacımız; CABG hastalarında yapılan PFT ile bu oranlar arasında bir ilişki olup olmadığını araştırmaktır.*

YÖNTEM ve GEREÇLER: *Bu retrospektif çalışmada Ocak 2014 ile Austos 2015 tarihleri arasında merkezimizde CABG uygulanan hastaların verilerini değerlendirilmiştir. CABG uygulanan hastaların demografik özellikler, kan sayımları, NLR, PLR, SIII ve PFT sonuçları kayıt altına alınarak değerlendirilmiştir.*

BULGULAR: *CABG uygulanan 61 hastanın verileri değerlendirildi. NLRile FEV1/FVC ve NLR ile MMEF75-25 arasında negatif yöne bir korelasyon tespit edildi (p<0.01).NLR için MMEF 75-25 < %80 ve FEV1/FVC<%80 olduğunda cut-off değeri belirlemek için ROC analizi yapıldı ve cut off değeri 2.105 olarak belirlendi (Sensitivity %67 ve specificity % 73)*

TARTIŞMA ve SONUÇ: *Respiratuar hastalık öyküsü olmayan ve CABG uygulanacak hastalarda NLR pılmoner fonksiyon testleri ine ters yönlü bir korelasyon göstermektedir. Çalışmamız, tam kan sayımından türetilen basit bir biyomarker olan NLR ile pulmoner fonksiyon testleri ilişkisini ortaya koyan ilk çalışmadır.*

Anahtar Kelimeler: *Nötrofil, lenfosit, pulmoner fonksiyon, CABG*

ABSTRACT

INTRODUCTION: *Pulmonary Function Tests (PFT) are important and frequently used for the preoperative evaluation of patients that will undergo cardiothoracic surgery and PFT are routinely required by anesthesiologists and surgical teams. Neutrophil Lymphocyte Ratio (NLR) is a biomarker recently reported by several studies to be associated with many diseases, and Platelet Lymphocyte Ratio and systemic immune inflammation index similarly. The aim of this study is to evaluate the presence of any correlation between PFT and theese ratios in patients without pulmonary disease or risk factors due to undergo CABG.*

METHODS: *The retrospective study was conducted at our hospital and performed by reviewing data of patients undergoing CABG between January 2014 and August 2015. Demographical features, echocardiological results, complete blood count results, ratios of NLR, PLR, SII and PFT results were evaluated in patients undergoing CABG.*

RESULTS: *Data of 61 patients were analyzed. A negative linear correlation was found between NLR and FEV1/FVC and NLR and MEF 75-25 % (p<0.01). ROC analysis was used to determine the cut off value for NLR when MMEF 75-25 < 80% and FEV1/FVC<80%. Cut off value of 2.105 was chosen for NLR with a sensitivity of 67.74% and specificity of 73.33% for FEV1/FVC <80% and sensitivity of 68.75% and specificity of 75.86% for MMEF75-25 <80%.*

DISCUSSION and CONCLUSION: *In patients without respiratory disease, due to undergo CABG, NLR shows an inverse correlation with PFT results. Our study is the first to put forth simple biomarkers calculated from CBC that can predict PFT.*

Keywords: *Neutrophil, lymphocyt, pulmonary function, coronary arter bypass greft surgery*

İletişim / Correspondence:

Dr. Serkan Tulgar
Maltepe Üniversitesi Tıp Fakültesi, Anestezi ve Reanimasyon Kliniği, İstanbul, Türkiye
E-mail: serkantulgar.md@gmail.com
Başvuru Tarihi: 29.04.2017
Kabul Tarihi: 11.07.2017

INTRODUCTION

Pulmonary Function Tests (PFT) are important and frequently used for the preoperative evaluation of patients that will undergo cardiothoracic surgery (1,2). PFT not only determine patients' pulmonary capacities but also give information about the presence of obstructive or restrictive pulmonary diseases and the health of large, medium and small airways (3-5).

While postoperative pulmonary complications (PPC) are seen in 2-9% of patients undergoing non cardiothoracic surgeries, this ratio is reported to be 8-39% for patients undergoing cardiothoracic surgery. Therefore, PFT are routinely required by anesthesiologists and surgical teams of patients due to undergo coronary artery bypass grafting or other cardiothoracic surgeries. Risk factors for PPC include COPD, smoking, age, pulmonary hypertension and obstructive sleep apnea (6). Congestive heart failure has a negative effect on PFT through mechanisms such as interstitial edema, hyper responsiveness due to changes in airway mucosa and decreased airway cross-section (7).

Neutrophil Lymphocyte Ratio (NLR) is a biomarker reported by several studies to be associated with heart failure and other cardiac diseases (8-12). Some studies have also reported a correlation between changes in NLR and respiratory diseases such as obstructive sleep apnea and COPD (13-17). Platelet lymphocyte ratio (PLR) and systemic immune inflammation index (SII) have also been the subject of research in many pathologies (8,18-22).

The aim of this study is to evaluate the presence of any correlation between NLR and PFT in patients without pulmonary disease or risk factors due to undergo CABG. As biochemical markers such as NLR have been demonstrated to change with the severity of systemic diseases, a correlation between NLR and PFT was foresawn.

MATERIAL and METHOD

This retrospective study was performed by reviewing data of patients undergoing CABG at a tertiary university hospital between January 2014 and August 2015. All patients' age, gender, preoperative anesthesiology evaluation data, laboratory results, smoking status, medication use, medical history, preoperative echocardiography findings and preoperative PFT data was collected. Patients with a history of pulmonary disease, hypertension, metabolic syndrome, diabetes mellitus or other systemic diseases and those on steroids were excluded from the study. CBC measurements were performed using Sysmex XT 1800i (Sysmex, Munich, Germany) according to quality standards. Patients with CBC data from another center were excluded. Variables analyzed for this study were age, gender, ejection fraction, NLR, PLR, SII, Forced expiratory volume (FEV) 1 %, forced expiratory vital capacity (FVC) %, FEV1/FVC % and maximum midexpiratory flow MMEF) 75-25 %. SII was calculated using the following formula: platelet count x neutrophil count/lymphocyte count.

Statistical analysis was performed using IBM SPSS Statistics v22.0. Descriptive variables are reported as average and standard deviation. Quantitative data was compared using Student t test for data showing normal distribution and Mann Whitney U test for data that was not normally distributed. Correlation between groups was analyzed using Pearson's correlation analysis. ROC analysis was used to evaluate the relationship between NLR and pulmonary function capacity. Cut off levels were determined by calculation of sensitivity and specificity at different points. Statistical significance was accepted as $p < 0.05$.

RESULTS

One hundred and thirteen patients' data were analyzed and the data of 61 patients who met inclusion criteria were retrospectively analyzed. Patients' average age was 61.95±10.49 (range 44 - 86) years. Female to male ratio was 9/52. Patients were evaluated as being American Society of Anesthesiology (ASA) score 2 and 3. Average left ventricular end diastolic ejection fraction was 53.85%±8.13% (median: 55%)

Average NLR was calculated as 2.12±0.65 (med 2.10), PLR 122.95±47.99 (med: 114.85) and SII was calculated as 554.55±257.28 (med: 514.79). A negative linear correlation was found between NLR and FEV1/FVC ($p=0.002$, $r=-0.393$); NLR and FEV 1 % ($p=0.011$, $r=-0.323$); and NLR and MEF 75-25 % ($p=0.002$, $r=-0.394$). No correlation was

found between NLR and FVC. Linear correlation graphs are shown in Figures 1 and 2.

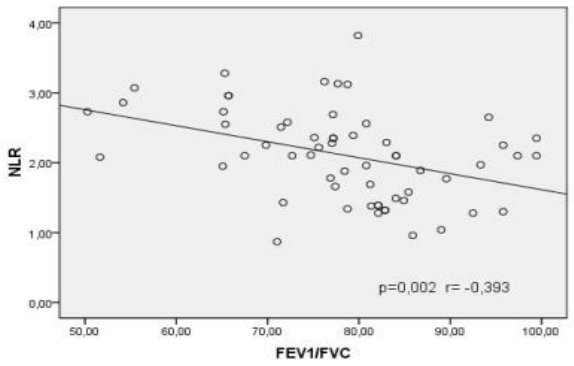


Figure 1. Correlation between NLR and FEV1/FVC

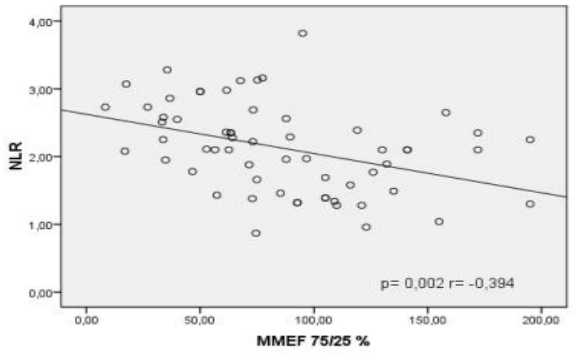


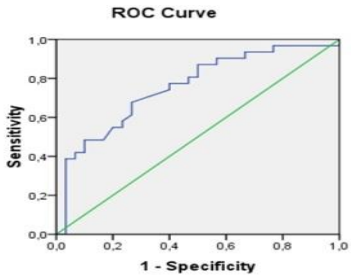
Figure 2. Correlation between NLR and MMEF 75-25%

A negative linear correlation was detected between PLR and FEV1/FVC (p=0.018, r=-0.303) while there was no correlation between PLR and FVC (p=0.280, r: 0.121); PLR and FEV 1 % (p=0.122, r=-0.200) or PLR and MEF 75-25 % (p=0.056, r=-0.246).

A negative linear correlation was found between SII and FEV1% (p=0.018, r=-0.303) and SII and FVC (p=0.026, r=-0.285). No correlation was found between SII and FEV/FVC (p=0.088, r:- 0.222) or SII and MEF 75-25 % (p=0.056, r=-0.246).

ROC analysis was used to determine the cutoff value for NLR when FEV1/FVC < 80%. ROC curve and area under curve is shown in Figure 3.

According to this data, cut off value of 2.105 was chosen for NLR with a sensitivity of 67.74% and specificity of 73.33%. At these values, the positive predictive value was 64.7% and negative predictive value was 66.66%. Patients with NLR > 2.105 were calculated to have a 3.66 times higher risk of FEV1/FVC < 80% (Odds ratio 3.666, 95% CI 1.2635-10.6404, p= 0.0168).



Diagonal segments are produced by ties.

Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
,755	,063	,001	,633	,878

Figure 3. ROC curve for NLR & FEV1/FVC and area under curve

ROC analysis was used to determine the cut off value for NLR when MMEF 75/25 < 80%. ROC curve and area under curve is shown in Figure 4. According to ROC curve, cut off value of 2.105 was chosen for NLR with a sensitivity of 68.75% and specificity of 75.86%. At these values, the positive predictive value was 71.87% and negative predictive value was 62.06%. Patients with NLR > 2.105 were calculated to have a 4.18 times higher risk of FEV1/FVC < 80% (Odds ratio 4,181, 95% CI 1.4266-12.2579, p= 0.0091).

DISCUSSION

Our study detected an inverse linear correlation between NLR and FEV1/FVC %, NLR and FEV 1 %, NLR and MMEF 75-25%, PLR and FEV1/FVC, SII and FEV1 and SII and FVC. With these findings it appears that a high NLR can be used as a biomarker for predicting patients with FEV1/FVC and MMEF 75-25% < 80%, in patients with no respiratory pathologies. Our study is the first to evaluate the relationship between NLR, PLR and SII and PFT. Even in patients with no diagnosed pulmonary pathology, respiratory problems are common in those that will undergo CABG, due to their underlying cardiac problems. Such patients may present with restrictive or obstructive patterns and sometimes with bronchial hyperactivity (2,7,23).

Undiagnosed cardiac or respiratory problems in CABG patients are important for postoperative respiratory complications and are an important risk factor for respiratory complications during anesthesia induction and maintenance (24). Therefore, preoperative SFT is important for

predicting respiratory dysfunction in patients undergoing cardiothoracic surgery.

Nazemiyeh et al (7) evaluated the relationship between pulmonary dysfunction in patients with congestive heart failure and Prohormone Brain Natriuretic Peptide (NTproBNP) and found an inverse linear correlation value between NTproBNP and FEV1, FVC, MMEF and LVEF, and a positive linear correlation between NTproBNP and FEV1/FVC. NTproBNP is used to determine the severity of heart failure and it has been found to be an important predictor for distinguishing heart failure related respiratory dysfunction. In our study we included all CABG patients without discriminating between those with or without heart failure. Therefore; we aimed to determine respiratory dysfunctions which were unpredictable. We detected an inverse correlation between respiratory dysfunctions and NLR which is basically calculated from CBC.

Yang et al (25) evaluated the demographics, glucose, white blood count (WBC), C-reactive protein, health status survey and PFT in more than 16 thousand adult patients. They found an inverse correlation between WBC and FEV 1%. We also used CBC data in our study, however we used more up-to-date systemic indexes (NLR, PLR, SII). Although we were unable to find a correlation with WBC, we determined that NLR is an effective method in predicting respiratory dysfunction. While Yang et al's study included patients over 18 years of age, we only included patients due to undergo CABG.

We were unable to find a report in literature on a biomarker or index used to correlate with PFT results. It has been reported that NLR is associated with severity in obstructive sleep apnea syndrome and that NLR is higher in severe OSAS patients when compared to mild or moderate severities (14). Also, NLR has been shown to be higher in stable COPD patients when compared to healthy controls and even higher in patients with COPD exacerbations when compared to stable COPD patients (16).

This study found an inverse relationship between NLR and PFT. While this study was performed on patients undergoing CABG, there are a group of patients with cardiac pathologies that require anesthesia for non-cardiac surgery. In these patients, NLR may be clinically used to determine which patients require PFT before as part of their preoperative evaluation.

Our study has some limitations that require mentioning. Our study is cross sectional and retrospective, therefore the demographic features may not show equal distribution. The number of our patients is relatively small. Our results could have been reinforced with a healthy control group. We also did not take into consideration the number of coronary arteries with stenosis, degree of stenosis, and time of medical treatment before surgery in our CABG patients. These variable conditions may have an effect on our results.

CONCLUSION

In patients without respiratory disease, due to undergo CABG, NLR shows an inverse correlation with PFT results and is therefore an important biomarker for the determination of preoperative respiratory dysfunction. Our study is the first to put forth simple biomarkers calculated from CBC that can predict PFT. When our limitations are taken into consideration, a larger randomized cohort with a control group is necessary to better understand and evaluate this relationship.

REFERENCES:

1. Kaza AK, Mitchell JD. Preoperative pulmonary evaluation of the thoracic surgical patient. Thorac Surg Clin 2005; 15:297–304.

2. Shapira N, Zabatino SM, Ahmed S, et al. Determinants of pulmonary function in patients undergoing coronary bypass operations. Ann Thorac Surg 1990; 50:268–73.

3. Mehari A, Afreen S, Ngwa J, et al. Obesity and Pulmonary Function in African Americans. PLoS One 2015; 10:e0140610.

4. Jones RL, Nzekwu M-MU. The effects of body mass index on lung volumes. Chest 2006; 130:827–33.

5. Sun LY, Gershon AS, Ko DT, et al. Trends in Pulmonary Function Testing Before Noncardiothoracic Surgery. JAMA Intern Med 2015; 175:1410–2.

6. Bapoje SR, Whitaker JF, Schulz T, et al. Preoperative evaluation of the patient with pulmonary disease. Chest 2007; 132:1637–45.

7. Nazemiyeh M, Sharifi A, Amiran F, et al. Relationship Between Prohormone Brain Natriuretic Peptide (NT-proBNP) Level and Severity of Pulmonary Dysfunction in Patients With Chronic Congestive Heart Failure. J Cardiovasc Thorac Res 2015; 7:24–7.

8. Durmus E, Kivrak T, Gerin F,et al. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio are Predictors of Heart Failure. Arq Bras Cardiol 2015; 105:606–13.

9. Özpelit E, Akdeniz B, Özpelit ME, et al. Prognostic value of neutrophil-to-lymphocyte ratio in pulmonary arterial hypertension. J Int Med Res 2015; 43:661–71.

10. Hyun S, Kwon S, Cho S, et al. Can the Neutrophil-to-Lymphocyte Ratio Appropriately Predict Carotid Artery Stenosis in Patients with Ischemic Stroke?-A Retrospective Study. J Stroke Cerebrovasc Dis 2015; 24:2646–51.

11. Kurtul S, Sarli B, Baktir AO, Demirbas M, Saglam H, Doğan Y, et al. Neutrophil to lymphocyte ratio predicts SYNTAX score in patients with non-ST segment elevation myocardial infarction. Int Heart J 2015; 56:18–21.

12. Benites-Zapata VA, Hernandez AV, Nagarajan V, et al. Usefulness of neutrophil-to-lymphocyte ratio in risk stratification of patients with advanced heart failure. Am J Cardiol 2015; 115:57–61.

13. Altintas N, Çetinoğlu E, Yuceege M, et al. Neutrophil-to-lymphocyte ratio in obstructive sleep apnea; a multi center, retrospective study. Eur Rev Med Pharmacol Sci 2015; 19:3234–40.

14. Taylan M, Demir M, Kaya H, et al. Alterations of the neutrophil-lymphocyte ratio during the period of stable and acute exacerbation of chronic obstructive pulmonary disease patients. Clin Respir J. 2017; 11:311-7

15. Yasar Z, Buyuksirin M, Ucsular FD, et al. Is an elevated neutrophil-to-lymphocyte ratio a predictor of metabolic syndrome in patients with chronic obstructive pulmonary disease. Eur Rev Med Pharmacol Sci 2015; 19:956–62.

16. Günay E, Sarınç Ulaşlı S, Akar O, et al. Neutrophil-to-lymphocyte ratio in chronic obstructive pulmonary disease: a retrospective study. Inflammation 2014; 37:374–80.

17. Sørensen AK, Holmgaard DB, Mygind LH, et al. Neutrophil-to-lymphocyte ratio, calprotectin and YKL-40 in patients with chronic obstructive pulmonary disease: correlations and 5-year mortality – a cohort study. J Inflamm 2015; 12:20.

18. Wu G, Yao Y, Bai C, et al. Combination of platelet to lymphocyte ratio and neutrophil to lymphocyte ratio is a useful prognostic factor in advanced non-small cell lung cancer patients. Thorac Cancer 2015; 6:275–87.

19. Hong X, Cui B, Wang M, et al. Systemic Immune-inflammation Index, Based on Platelet Counts and Neutrophil-Lymphocyte Ratio, Is Useful for Predicting Prognosis in Small Cell Lung Cancer. Tohoku J Exp Med 2015; 236:297–304.

20. Yang Z, Zhang J, Lu Y, et al. Aspartate aminotransferase-lymphocyte ratio index and systemic immune-inflammation index predict overall survival in HBV-related hepatocellular carcinoma patients after transcatheter arterial chemoembolization. Oncotarget 2015; 6:43090–8.

21. Koh C-H, Bhoo-Pathy N, Ng K-L, et al. Utility of pre-treatment neutrophil–lymphocyte ratio and platelet–lymphocyte ratio as prognostic factors in breast cancer. Br J Cancer 2015; 113:150–8.

22. Akdag S, Akyol A, Asker M, et al. Platelet-to-Lymphocyte Ratio May Predict the Severity of Calcific Aortic Stenosis. Med Sci Monit 2015; 21:3395–400.

23. Sasaki F, Ishizaki T, Mifune J, et al. Bronchial hyperresponsiveness in patients with chronic congestive heart failure. Chest 1990; 97:534–8.

24. Güler M, Kirali K, Toker ME, et al. Different CABG methods in patients with chronic obstructive pulmonary disease. Ann Thorac Surg 2001; 71:152–7.

25. Yang H-F, Kao T-W, Wang C-C, et al. Serum white blood cell count and pulmonary function test are negatively associated. Acta Clin Belg 2015; 70:419–24.