Original Article

Neutrophil/Lymphocyte Ratio Can Predict Postoperative Mortality in Patients with Chronic Thromboembolic Pulmonary Hypertension

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Objective: The aim of our study was to investigate clinical importance of neutrophil/lymphocyte ratio in patients with Chronic thromboembolic pulmonary hypertension.
Methods: 125 consecutive patients with a diagnosis of Chronic thromboembolic pulmonary hypertension were operated pulmonary thromboendarterectomy in our center between February 2011 and August 2013. 106 patients included into the study due to limitations. The patients were classified into two groups as patients discharged alive (Group 1) and those dying in the hospital (Group 2). Baseline neutrophil/lymphocyte ratio level was measured by dividing neutrophil count to lymphocyte count.
Results: 84 patients (79%) were in Group 1, 22 patients (21%) were in Group 2. Patients with higher neutrophil/lymphocyte ratio in admission have a significantly higher mortality rate and postoperative pulmonary vascular resistance was found statistically significant variable to predict the mortality. Receiver operator characteristic (ROC) analysis revealed that using a cut-off point of 2.54, admission neutrophil/lymphocyte ratio predicts mortality. Also, correlation analysis showed a significant correlation between preoperative pulmonary vascular resistance and neutrophil/lymphocyte ratio.
Conclusion: The neutrophil/lymphocyte ratio level may be a useful and noninvasive biomarker for operative risk stratification for mortality after pulmonary thromboendarterectomy.

Keywords: Chronic thromboembolic pulmonary hypertension, pulmonary thromboendarterectomy, pulmonary vascular resistance, inflammation, Neutrophil/lymphocyte ratio.

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Introduction

Pulmonary arterial hypertension (PAH) is a disease associated with high morbidity and mortality. Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the main causes of PAH which is a progressive disease leading to right heart failure and low cardiac output, finally leads to death if left untreated.[1] CTEPH is described by fibrotic obstruction of proximal and/or distal pulmonary arteries due to organized thrombus by doing distal arteriopathy in small pre-capillary pulmonary vessels and hence it increases the pulmonary vascular resistance (PVR).[1–3] Previous studies demonstrated that PVR is one of the most important hemodynamic parameter in CTEPH patients.[2] The increased PVR is mainly caused by endothelial

dysfunction, vascular remodeling, vasoconstriction, thrombosis and fibrosis of distal pulmonary arteries.[4] It's known that there is increased prevalence of inflammatory disease in CTEPH patients.[3–5] Recently, there are increasing evidences for the role of inflammation in pathophysiologic mechanisms of CTEPH.[3] When investigated the role of inflammation in these patients, elevated levels of inflammatory cytokines are detected in the lung biopsies[6] and the plasma samples.[7,8] Also C-reactive protein (CRP) level is found significantly higher in patients with CTEPH compared with healthy subjects (p <0.01).[9] However, the clinical importance of inflammatory state in CTEPH patients have not been well clarified so far. The neutrophil/lymphocyte ratio (NLR) is a new inflammatory biomarker and can be used as an indicator of systemic inflammation in many disease.[10–12] The aim of our study was to investigate clinical importance of NLR in patients with CTEPH.

Materials and Methods

125 consecutive patients with a diagnosis of CTEPH were operated pulmonary thromboendarterectomy (PEA) in our center between February 2011 and August 2013. Patients with hepatic or renal insufficiency, previous coronary artery bypass grafting, heart failure (left ventricular ejection fraction [LVEF] <40%), malignancy (pulmonary sarcoma), known chronic systemic inflammatory disease (Behçet's disease, systemic lupuserythematosus, poliomyelitis, ulcerative colitis, Takayasu vasculitis), were excluded from the present study. 106 eligible patients (64 females, range 18–78 years) were included into the study.

Clinical information including age, sex, body surface area (BSA), history of hypertension and diabetes mellitus, smoking, current medications, complete blood count, CRP levels and biochemical parameters was obtained from a review of the patients' chart. Hematologic indices, such as hemoglobin, white blood cell and lymphocyte and neutrophil counts were measured as part of the automated complete blood count, using simultaneous optical and impedance measurements (Cell Dyn 3700 Abbott Diagnostics, Abbott Park, Illinois, USA). All routine biochemical tests were carried out on an automatic biochemical analyzer (Beckman Coulter AU640; Beckman Coulter, Krefeld, Germany). C-reactive protein (CRP) was determined by nephelometry on an IMMAGE® 800 analyzer (Beckman Coulter, Germany). The diagnosis of CTEPH was established on the basis of previously reported procedures.[13] Diagnosis and cardiopulmonary

hemodynamic characteristics were determined by 6 minute walking test (6MWT), computed tomography pulmonary angiography (CTPA) and right sided heart catheterization (RHC). Pulmonary hypertension was defined as mean pulmonary artery pressure (mPAP) greater than 25 mmHg. In all patients, normal left ventricular function was documented by echocardiography. Coronary angiography was routinely performed in all patients aged more than 40 years. Operative procedure was performed as explained with details in previous article.[14] Shortly, the operation was performed on deep hypothermia (20°C) for both lungs under complete circulatory arrest. A true endarterectomy was accomplished and, when it was completed on both sides, circulation with warming was restarted. Postoperative hemodynamic characteristics were determined on the first day after PEA. All investigations were approved by the local institutional review board. The patients were classified into two groups as patients discharged alive (Group 1) and those dying in the hospital (Group 2). Baseline NLR level was measured by dividing Neutrophil count to lymphocyte count.

Statistical analysis

Kolmogorov—Smirnov normality test was used to determine whether the continuous random variables are normally distributed or not. For the continuous random variables unpaired t-test and for discrete random variables Chi-square test were applied for the comparisons between groups. A multivariate stepwise logistic regression was used to predict for independent predictors of mortality. A ROC analysis was implemented to assess the sensitivity and specificity of NLR to find a cut-off point and to calculate area under curve (AUC). Pearson Correlation Coefficient was calculated to determine any relationship between two continuous variables. Statistical analysis was carried out using SPSS software (version 15.0) for Windows (SPSS, Chicago, Illinois, USA). P <0.05 was considered as "significant".

Results

The one hundred and six patients included into the study. Patients were divided into 2 groups as patients discharged alive in the hospital (Group 1) and those died in hospital period (Group 2). The eighty-four patients (79%) were in Group 1, twenty two patients (21%) were in Group 2. A comparison of groups regarding baseline characteristics and laboratory data shown in **Table 1** and comparison of perioperative hemodynamic values

Table 1   Comparison of clinical characteristics and laboratory data in the groups

Variables	Group1 Mortality (−) (n = 84)	Group2 Mortality (+) (n = 22)	*p value
Clinical Characteristics			
Age (years)	48.8 ± 13.9	50.7 ± 12.7	0.572
Body surface area	1.9 ± 0.20	1.8 ± 0.1	0.472
Gender (n,%, male)	31 (37)	11 (50)	0.384
Hypertension (n,%)	33 (39)	11 (50)	0.506
Diabetes Mellitus (n,%)	12 (14)	5 (23)	0.526
Smoking (n,%)	22 (26)	9 (41)	0.195
CAD (n,%)	4 (5)	3 (14)	0.155
6MWT (metres)	272.5 ± 123.1	253.6 ± 105.9	0.512
NYHA 3–4 (n,%)	58 (69)	158 (82)	0.181
Respiratory and Echocardiographic Datas			
FEV1	78.9 ± 18.1	73.7 ± 12.5	0.206
FVC	82.7 ± 16.8	79.1 ± 17.0	0.376
FEV1/FVC	0.95 ± 0.11	0.94 ± 0.10	0.662
LVEF	62.9 ± 3.9	62.3 ± 3.3	0.440
PAPs	68.7 ± 26.4	83.3 ± 25.6	0.022
TAPSE	15.9 ± 4.4	11.7 ± 3.4	<0.001
Hematologic and Biochemical Laboratory Datas			
Urea (mg/dL)	39.0 ± 16.9	40.1 ± 13.1	0.772
Creatinine (mg/dL)	0.85 ± 0.27	0.85 ± 0.18	0.916
Hemoglobin (gr/dL)	13.2 ± 1.9	13.9 ± 2.0	0.206
Hematocrit (gr/dL)	40.4 ± 5.8	42.2 ± 5.6	0.181
Red cell distribution width (%)	17.8 ± 3.9	17.9 ± 3.0	0.963
Red Blood Cell (×10³/mm³)	4.9 ± 0.6	4.9 ± 0.7	0.924
Platelet Counts (×10³/mm³)	266.8 ± 98.0	191.1 ± 47.9	<0.001
Platelet Distribution Width (%)	29.8 ± 17.7	29.5 ± 18.4	0.952
Mean Platelet Volume (fl)	8.6 ± 1.5	8.3 ± 1.3	0.428
WBC Count (×10³/μL)	7.6 ± 2.3	7.7 ± 2.2	0.807
Neutrophil Counts (×10³/mm³)	4.8 ± 1.7	5.8 ± 2.1	0.019
Lymphocyte Counts (×10³/mm³)	2.0 ± 0.8	1.2 ± 0.6	<0.001
NLR	2.6 ± 1.3	6.1 ± 3.9	<0.001
Eosinophil Counts (×10³/mm³)	0.17 ± 0.15	0.13 ± 0.31	0.401
Basophil Counts (×10³/mm³)	0.05 ± 0.03	0.04 ± 0.02	0.089
ESR	22.5 ± 18.0	18.7 ± 16.1	0.367
CRP	2.02 ± 1.73	2.80 ± 1.98	0.071

Variables are expressed as mean ± standard deviation and percentage (%) for categorical variables. * Unpaired Student-t and Chi-square tests. CAD: coronary artery disease; 6MWT: 6 minutes walking test; NYHA: New York Heart Association; FEV: force expiratory volume; FVC: force vital capacity; LVEF: left ventricular ejection fraction; PAPs: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion; WBC: white blood cell; NLR: neutrophilto lymphocyte ratio; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

is presented in **Table 2**. There was no statistically significant difference between the two groups with respect to age, gender, coronary artery disease risk factors. While white blood cell (WBC) and hemoglobin values were found to be insignificant between two groups, lymphocyte count was significantly lower and neutrophil count and NLR level was significantly higher in Group 2 patients (**Table 1**). Among operating times, while cross-clamp time was found to be insignificant, total perfusion time was found to be significantly longer in Group 2 than in Group 1 (**Table 2**).

Tricuspid Annular Plane Systolic Excursion (TAPSE), preoperative Cardiac output, Cardiac index, mean pulmonary arterial pressure, platelet level, neutrophil level, lymphocyte level, NLR, duration of totally perfusion time (minutes) (TPT), preoperative PVR and postoperative PVR, which were found significant as independent predictors of mortality in univariate analyses (**Tables 1–2**), were used to perform multivariate logistic regression analysis (**Table 3**). Despite systolic systemic arterial pressure (SAPs), systolic pulmonary arterial pressure (PAPs) and diastolic pulmonary arterial pressure (PAPd) variables

Table 2   Comparison of perioperative hemodynamic values and operating times in the groups

Variables	Group 1 Mortality (–) (n = 84)	Group 2 Mortality (+) (n = 22)	*pValue
TPT	185.9 ± 40.1	225.5 ± 68.4	0.015
ACC	74.3 ± 37.7	67.5 ± 42.8	0.467
Major Bleeding	5 (6)	2 (9)	0.633
Preop PVR	893.1 ± 346.7	1130.8 ± 375.0	0.006
Postop PVR	386.9 ± 157.2	560.4 ± 229.7	0.001
Diff PVR	510.8 ± 348.6	558.4 ± 468.7	0.676
SVR	1680.3 ± 516.5	1793.1 ± 542.2	0.369
Preop CO	4.3 ± 1.4	3.2 ± 0.7	<0.001
Postop CO	6.0 ± 2.0	4.9 ± 2.4	0.118
CI	2.3 ± 0.7	1.8 ± 0.4	<0.001
PAPs	71.7 ± 26.9	86.8 ± 21.4	0.017
PAPd	29.8 ± 14.3	34.6 ± 8.3	0.046
PAPm	43.7 ± 17.5	51.9 ± 11.3	0.011
SAPs	127.2 ± 18.7	117.7 ± 15.4	0.031
SAPd	74.5 ± 13.2	71.0 ± 10.4	0.253
SAPm	92.1 ± 13.5	86.6 ± 10.7	0.081
Pulm Saturation	60.6 ± 9.8	56.2 ± 11.5	0.195
Sist Saturation	90.7 ± 5.0	89.2 ± 5.3	0.342
PCWP	11.7 ± 3.1	11.1 ± 2.7	0.411

TPT: duration of totally perfusion time (minutes); ACC: aortic cross clamping time; PVR: pulmonary vascular resistance; Diff PVR: The gap between preoperative and postoperative PVR values; SVR: systemic vascular resistance; CO: cardiac output; CI: cardiac index; PAPs: systolic pulmonary arterial pressure; PAPd: diastolic pulmonary arterial pressure; PAPm: mean pulmonary arterial pressure; SAPs: systolic systemic arterial pressure; SAPd: diastolic systemic arterial pressure; SAPm: mean systemic arterial pressure; PCWP: pulmonary capillary wedge pressure

Table 3   Determination of significant independent predictors of mortality after performing multivariate logistic regression analyses

	B	S.E.	Wald	df	Sig	OR = Exp (B)	95 % CI. For EXP (B) Lower	95 % CI. For EXP (B) Upper
NLR	1.018	0.336	9.177	1	0.002	2.767	1.432	5.347
Postop PVR	0.007	0.003	7.332	1	0.007	1.007	1.002	1.013
TPT	0.022	0.010	5.053	1	0.025	1.022	1.003	1.042
Constant	–13.139	3.717	12.496	1	0.000	0.000		

a. Variable(s) entered on step 1: NLR. (first important variable and statistically significant to predict the presence or absence of mortality). b. Variable(s) entered on step 3: TPT. (second important variable and statistically significant to predict the presence or absence of mortality). c. Variable(s) entered on step 2: POSTOP.PVR. (thirth important variable and statistically significant to predict the presence or absence of mortality). NLR: neutrophilto lymphocyte ratio; PVR: pulmonary vascular resistance; TPT: duration of totally perfusion time (minutes)

are significant in univariate analysis, these are excluded in multivariate analysis firstly in order not to increase the number of independent variables unneccesarily, secondly due to the close relation between cardiac output (CO), cardiac index (CI) and SAPs and thirdly mean pulmonary arterial pressure (PAPm) value is calculated by using PAPs and PAPd values. According to this analysis; goodness of fit test, Nagelkerke R Square, Hosmer and Lemeshow Test and Classification Table Percentage were found respectively as: p <0.0001, 55.5%, p >0.05 (p = 0,968) and 91%. Therefore, patients with higher NLR in admission have a significantly higher mortality rate HR (hazard ratio): 2.767; 95% CI: 1.432–5.347; p = 0.002), TPT and postoperative PVR were found as second and third statistically significant variables to predict the presence or absence of mortality (respectively, p = 0.0025, p = 0.007).
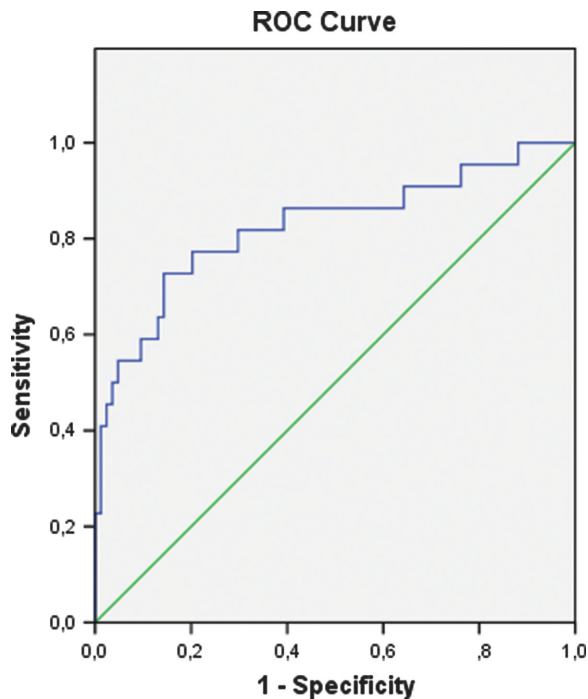
ROC Curve

AUC: 0.825 SE: 0.058

Fig. 1 ROC curve analysis of NLR predicts mortality. ROC: receiver operator characteristic; NLR: the neutrophil/lymphocyte ratio; AUC: area under curve.

ROC analysis revealed that using a cut-off point of 2.54, admission NLR predicts mortality with a sensitivity of 86% and specificity of 40% in CTEPH patients treated with PEA (**Fig. 1**). The area under the curve for this relationship is 0.825 and the 95% CI is 0.713–0.938. When patients divided with regard to cut off value, mean PVR is 872 ± 350 dyne · s · cm^{-5} in patients who have NLR lower than 2.54 and that is 1012 ± 367 dyne · s · cm^{-5} in patients who have NLR upper than 2.5 (p = 0.048).

Also, correlation analysis showed a significant correlation between preoperative PVR and NLR (r = 0.214, p = 0.027).

Discussion

This is the first study in CTEPH patients in which we demonstrated that clinical use of NLR may be a noninvasive parameter for preoperative risk stratification of CTEPH patients. We showed that higher NLR level is associated with higher morbidity and mortality rate in patients with CTEPH who was operated PEA. Moreover we have shown that NLR value is an independent predictor of mortality in these patients. And also preoperative PVR is correlated with preoperative NLR.

One of the most important causes of PAH is CTEPH which is surgically curable.[15] PEA is an effective and ideal therapeutic choice in CTEPH patients. It dramatically decreases PVR and leads to a significant healing of bad course. Nevertheless, the postoperative course is associated with significant morbidity and mortality. The postoperative mortality rate is remarkable and ranges from 1.3 to 24%.[16] Previously researches have been demonstrated that severely affected patients, i.e. mPAP >50 mmHg, cardiac index <2.0 l/min m^2, pulmonary vascular resistance >1000 dynes · s · cm^{-5} and/or New York Heart Association class IV disease, are at high risk for postoperative bad course and mortality after PEA.[17,18] Among them, preoperative PVR is found the most important predictor of outcome after PEA.[17,18] While mortality rate is 4% in patients who have preoperative PVR <900 dyne · s · cm^{-5}, that is 10% in patients who have preoperative PVR 900–1200 dyne · s · cm^{-5} and that is 20% in patients who have preoperative PVR >1200 dyne · s · cm^{-5}.[17] Also, Jamiesson, et al. showed that postoperative PVR (more than 500 dyne · s · cm^{-5}) is found as an independent predictor for mortality.[18] In our study we showed that while preoperative and postoperative PVR is associated with mortality, only postoperative PVR is an independent predictor of mortality. Moreover, by using logistic regression analysis, we demonstrated that preoperative NLR and TPT are independent predictors of mortality too.

As is well known, the increased PVR in patients with CTEPH is mainly caused by endothelial dysfunction, vasoconstriction, vascular remodeling and proliferation, thrombosis and fibrosis of small and distal pulmonary arteries.[8,19] There is increasing evidence of inflammation which plays an important role in the pathophysiology of PVR with elevated levels of many cytokines and chemokines in affected patients.[20,21] Also, inflammatory cell infiltrates had been observed around the distal vascular area.[8] It is now considered to be a distal vasculopathy, in which structural changes caused by vascular remodeling and inflammation play a major role.[6–19] However, the pathophysiologic mechanism of increased PVR has not been well clarified so far.

White blood cell subtypes such as neutrophil and lymphocyte have an important role in modulating the inflammatory response in the PAH pathogenesis. Particularly, lymphocytopenia and neutrophilia are common findings in inflammatory states.[19] As NLR reflects the balance between neutrophil and lymphocyte levels, it is an indicator of systemic inflammation.[6,15] Increased NLR has

been shown to be related to short and long term outcomes in various cardiac diseases.[10–12] In particular, it is determined that NLR is a predictor of short term mortality in acute pulmonary embolism.[11]

Circulating monocyte chemoattractant protein-1 has been found to correlate with PVR in CTEPH patients.[22] Our findings confirm and contribute previous studies, in which used different inflammatory biomarkers, on the usefulness of NLR to correlate preoperative PVR and also to predict mortality.[9,23] In addition, NLR was positively correlated with PVR, supporting the hypothesis that inflammation is an important process on PVR in patients with CTEPH.

In our study we found that, the level of NLR ≥2.54 predicted the risk of mortality in CTEPH patients after PEA with 86% sensitivity and 40% specificity. Moreover the defined cut-off level of NLR was reflected preoperative PVR. As preoperative PVR was 872.6 ± 350 dyne $\cdot$ s $\cdot$ cm^{-5} in patients who have NLR <2.54 that was 1012.2 ± 367.7 dyne $\cdot$ s $\cdot$ cm^{-5} in patients who have NLR ≥2.54.

While NLR was significantly elevated in the mortality group, CRP levels did not statistically differ between the groups. Quarck, et al. stated that CRP could not be identified as a prognostic factor to predict adverse outcome of PEA in CTEPH patients.[9] Hence, we do not expect any relation between mortality and CRP.

There are some limitations to this study that need to be addressed. First is this study represents a small number of patients. In this study, most of the patients were treated preoperatively with antiPAH drugs till surgery. The second point is the effects of medical treatment on NLR levels were not determined. The thirth one is inflammatory markers except CRP were not analyzed and compared with the NLR. Lastly, this is a retrospective study. Therefore, a prospectively designed larger study should be performed to highlight the clinical importance and application of measurements of NLR in CTEPH patients.

Conclusion

We suggest that the NLR level may be a useful and noninvasive biomarker for operative risk stratification for mortality in early postoperative period after PEA. In addition to the preoperative NLR is correlated with preoperative PVR values, patients with higher NLR than 2.5 have higher preoperative PVR than 1000 dyne $\cdot$ s $\cdot$ cm^{-5}.

Disclosure Statement

Mehmed Yanartas, Cengiz Koksal and Serpil Gezer Tas serve as a consultant to Marmara University School of Medicine, department of Cardiovascular surgery, Akin Arslan serve as a research assistant to Medipol University Faculty of Medicine department of Cardiovascular Surgery, Nural Bekiroglu serve as a consultant to Marmara University School of Medicine Department of Biostatistic, Bedrettin Yildizeli serve as a consultant to Marmara University School of Medicine, department of Thoracic Surgery. All authors declare that there is no any conflict of interest.

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