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Value of the neutrophil-to-lymphocyte ratio in predicting post-pericardiotomy syndrome after cardiac surgery

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Abstract. – OBJECTIVE: Post-pericardiotomy syndrome (PPS) occurs in 10-40% of patients after cardiac surgery. PPS is considered an autoimmune phenomenon. The neutrophil-to-lymphocyte ratio (NLR) is a novel inflammatory marker that is associated with various cardiovascular diseases. Studies have reported that the NLR increases in certain autoimmune diseases. This study examined whether the NLR is helpful to predict the occurrence of PPS after elective on-pump coronary artery bypass graft (CABG) surgery.

PATIENTS AND METHODS: The records of patients who underwent elective first-time on-pump CABG were reviewed retrospectively. In total, 72 patients with PPS were included in the study, and 100 patients who did not develop PPS were included as the control group. Peripheral blood samples collected preoperatively and on postoperative day 1 were used to calculate the NLR.

RESULTS: No differences in preoperative white blood cell (WBC) count, neutrophil count, lymphocyte count, or NLR were observed between the patients with PPS and the control group. The WBC ($p < 0.001$) and neutrophil counts ($p < 0.001$) and NLR ($p = 0.01$) were significantly higher during the postoperative period in patients with PPS than in the control group. A receiver operating characteristic curve analysis showed that the postoperative NLR predicted PPS with 60% sensitivity and 59% specificity (area under the curve, 0.61; 95% confidence interval [CI], 0.51-0.70; $p = 0.017$), using a cut-off of 8.34. The postoperative WBC count (odds ratio [OR], 1.6; 95% CI, 1.36-2.03; $p < 0.001$) and NLR (OR, 3.3; 95% CI, 1.56-7.01; $p = 0.002$) were independently associated with PPS.

CONCLUSIONS: The postoperative NLR may be useful to predict the development of PPS in patients undergoing on-pump CABG.

Key Words:
Neutrophil-to-lymphocyte ratio, Post-pericardiotomy syndrome, Cardiac surgery.

Introduction

Post-pericardiotomy syndrome (PPS) is a common postoperative complication in patients who undergo cardiac surgery, and it remains an important cause of morbidity. PPS occurs in 10-40% of patients after cardiac surgery[1-4]. Pericardial effusion occurs due to surgical bleeding during postoperative week 1, but effusion occurring > 7 days postoperatively is usually associated with PPS and can result in cardiac tamponade, which may be life threatening[2]. Although the pathogenesis is not clearly established, PPS is considered an autoimmune phenomenon[5-7].

Previous studies have shown relationships between inflammatory markers and cardiovascular disease[8-10]. The neutrophil-to-lymphocyte ratio (NLR), a novel marker of systemic inflammation, is an integrated reflection of two important and opposite immune pathways and is more predictive than either parameter alone[11].

The NLR is associated with various cardiovascular diseases[12,13], and is an independent predictor of adverse outcomes in patients with cardiovascular disease; moreover, it is useful for predicting mortality following percutaneous coronary intervention and coronary artery bypass graft (CABG) surgery[14,15]. Previous studies have reported that the NLR increases in patients with certain autoimmune diseases and is positively

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correlated with the activities of diseases such as ulcerative colitis[16], primary Sjogren's syndrome[17], rheumatoid arthritis[18], Hashimoto's thyroiditis[19], Behcet's disease[20], and systemic lupus erythematosus[21].

Predicting the occurrence of PPS may allow measures to reduce postoperative morbidity and mortality related to PPS, decrease management costs, and improve the quality of life for patients. Only a few studies have examined the roles of biomarkers in identifying patients likely to develop PPS following cardiac surgery[22,23]. To date, no validated biomarkers with high sensitivity and high specificity have been established to diagnose PPS.

The purpose of this study was to examine whether the NLR is helpful to predict the occurrence of PPS after elective on-pump CABG. This is the first study to examine the relationship between the NLR and PPS after cardiac surgery.

Patients and Methods

Study Population

This study was approved by our local Ethics Committee and complied with the requirements of the Declaration of Helsinki. We retrospectively reviewed the medical records of patients who underwent elective first-time CABG with cardiopulmonary bypass (CPB) between January 2012 and January 2015. In total, 72 patients with PPS were included in the study. A total of 100 patients who did not develop PPS were used as a control group. The only inclusion criterion was a preoperative and postoperative complete blood count.

The exclusion criteria were: (1) renal failure, (2) hepatic failure, (3) hematological disorders, (4) rheumatic heart disease, (5) emergency procedures, (6) poor ventricular function, (7) redo-CABG, (8) off-pump CABG, (9) surgery within the first week after infarction, (10) perioperative myocardial infarction, (11) no postoperative echocardiography data available, (12) patients who had a postoperative effusion in the first week after surgery, (13) patients who received non-steroidal anti-inflammatory drugs (NSAIDs) during the perioperative period, (14) perioperative hemodynamic instability, (15) corticosteroid administration during the perioperative period, and (16) the presence of active or chronic inflammatory or autoimmune disease.

A diagnosis of PPS was established when patients met two of the following five criteria: unexplained postoperative fever lasting beyond postoperative week 1, pleuritic chest pain, pericardial or pleural friction rub, new pleural effusion, and new pericardial effusion after surgery[2].

Data Collection

Demographic, clinical, and laboratory parameters were collected from the patients' medical records. All chest X-rays and echocardiograms were reassessed. Patient temperatures were obtained from charts.

Transthoracic echocardiography and chest X-rays were performed before discharge and on postoperative day 15 ± 1 in all patients as part of the standard postoperative management protocol. The existence of pericardial effusion was determined by echocardiography. At our hospital, pericardial effusion is evaluated in all available echo windows and measured during the diastolic cardiac phase. The existence of pleural effusion was determined by a chest X-ray.

Aspirin was discontinued 1 week prior to surgery in all patients and was resumed 6-12 h postoperatively. The patients were not given NSAIDs postoperatively.

Blood Sampling

Peripheral blood samples collected preoperatively and on postoperative day 1 were used to calculate the NLR. All blood samples were collected in Becton-Dickinson Vacutainer tubes containing 3.6 mg of dipotassium ethylenediaminetetraacetic acid (Franklin Lakes, NJ, USA). An automatic blood counter (Sysmex XT 2000i Hematology Analyzer; Sysmex, Kobe, Japan) was used for the complete blood counts. Complete blood counts were performed within 1 h after sampling according to hospital policy.

Statistical Analysis

A statistical analysis was conducted using SPSS for Windows ver. 17 (SPSS Inc., Chicago, IL, USA). All variables were investigated using visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine the normality of the distribution. Continuous variables are reported as means and standard deviations for normally distributed variables, and as medians and the interquartile range for non-normally distributed variables. Categorical variables are presented as numbers and per-

centages. Comparisons between groups were performed using the chi-square test for qualitative variables, the independent *t*-test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed continuous variables. The capacity of the NLR to predict PPS was analyzed using a receiver operating characteristics (ROC) curve analysis. The area under the curve (AUC) was calculated as a measure of test accuracy. Sensitivity and specificity were presented when a significant cut-off value was observed. A logistic regression analysis was used to evaluate associations between the NLR and PPS; *p*-values < 0.05 were considered significant.

Results

A total of 72 patients with PPS were included in the study (50 males; median age, 60.5 years; range, 52.25–66). The control group consisted of 100 patients who underwent CABG (72 males; median age, 61 years; range, 54-67). The patients' clinical characteristics are presented in Table I.

The laboratory findings for both groups are presented in Table II. No significant difference in preoperative WBC count, neutrophil count, lymphocyte count, or NLR was observed between the patients with PPS and the control group. The WBC count ($p < 0.001$), neutrophil count ($p < 0.001$), and NLR ($p = 0.01$) were significantly higher in patients with PPS during the postoperative period than in the control group.

ROC Analysis

The ROC analysis showed that the postoperative NLR predicted PPS with 60% sensitivity and 59% specificity, using a cut-off value of 8.34. The AUC for the postoperative NLR was 0.61 (95% CI, 0.51-0.70; $p = 0.017$). The ROC curve of the NLR is shown in Figure 1. Patients with a postoperative NLR > 8.34 had a three-fold increased risk of developing PPS (OR, 3.26; 95% CI, 1.72-6.15; $p < 0.001$).

Multivariate Analysis

The cross-clamp time and CPB time correlated strongly (r = 0.61); therefore, only the CPB time was used in the multivariate models. The postoperative WBC count (OR, 1.6; 95% CI, 1.36-2.03; $p < 0.001$) and postoperative NLR (OR, 3.3; 95% CI, 1.56-7.01; $p = 0.002$) were independently associated with PPS in a model that included age, sex, CPB time, number of anastomoses, number of transfusions, postoperative WBC count, and postoperative NLR.

Discussion

We demonstrated that the postoperative WBC count and NLR were significantly higher in patients with PPS than in patients without PPS. We also found that the NLR was an independent predictor of PPS in patients undergoing CABG. This is the first report on the clinical significance of the NLR in patients with PPS.

Although the pathogenesis is not clearly established, PPS is an immune-mediated inflammatory process triggered by cardiac antigen expo-

Table I. Clinical characteristics of the patients.

	PPS (n = 72)	NO PPS (n = 100)	*p* value
Age, years, median (IQR)	60.5 (52.25-66)	61 (54-67)	0.8
Male, n (%)	50 (69.4)	72 (72)	0.7
HT, n (%)	49 (68)	73 (73)	0.48
DM, n (%)	18 (25)	34 (34)	0.2
HL, n (%)	39 (54.2)	52 (52)	0.78
Smoking, n (%)	40 (55.6)	49 (49)	0.39
COPD, n (%)	20 (27.8)	24 (24)	0.57
Operative data			
Number of anastomoses, mean ± SD	3.36 ± 1.07	3.26 ± 1.06	0.54
CPB time, min, mean ± SD	80.1 ± 21.9	78.8 ± 20.6	0.68
X clamp time, min, mean ± SD	55.9 ± 20.8	54.4 ± 20.6	0.63
Number of blood transfusion, median (IQR)	2 (1-3)	2 (1-3)	1
Drainage, ml, 24 hour	550 (350-750)	500 (250-700)	0.1

PPS: Postpericardiotomy syndrome; HT: Hypertension; DM: Diabetes mellitus; HL: Hyperlipidemia; COPD: Chronic obstructive pulmonary disease; CPB: Cardiopulmonary bypass.

Table II. Preoperative and postoperative laboratory results of the patients.

	PPS (n = 72)	NO PPS (n = 100)	*p* value
Preoperative laboratory data			
WBC, 109/L, mean ± SD	7.7 ± 1.27	7.35 ± 1.6	0.12
Neu count, 109/L, mean ± SD	4.8 ± 1.05	4.66 ± 1.3	0.42
Lymp count, 109/L, mean ± SD	2 ± 0.6	1.84 ± 0.55	0.67
NLR, median (IQR)	2.39 (1.8- 3.15)	2.6 (1.9-3.3)	0.35
Postoperative laboratory data			
WBC, 109/L, mean ± SD	14.1 ± 2.3	12 ± 1.86	< 0.001
Neu count, 109/L, median (IQR)	11.03 (9.5-13.31)	9.58 (7.78-10.75)	< 0.001
Lymp count, 109/L, median (IQR)	1.22 (0.94-1.85)	1.23 (1.08-1.54)	0.7
NLR, median (IQR)	8.65 (5.7-13.2)	7.55 (5.38-9.33)	0.01

PPS: Postpericardiotomy syndrome; WBC: White blood cell count; Neu: Neutrophil; Lymp: Lymphocyte; NLR: Neutrophil to lymphocyte ratio.

sure[5-7,24,25]. Engle et al[24] showed high titers of anti-heart antibodies in patients with PPS. Myocardial muscle injury during surgery leads to the release of auto-antigens. The release of these auto-antigens can trigger a host immune response and the production of anti-heart antibodies and immune complexes. De Scheerder et al[26] reported a significant correlation between developing PPS and an increase in the number of immune complexes. They also demonstrated a significant correlation between postoperative anti-heart antibodies and an increase in the number of immune complexes, suggesting a possible pathogenic role. Maisch et al[27] further examined the subtypes of specific autoantibodies and showed that 95% of their patients with PPS had antibodies to myocardium and skeletal muscle. Surgery and trauma were the proposed etiologies for the myocardial injury that caused the release of these myocardial antigens. Furthermore, cardiac surgery with CPB initiates a systemic inflammatory response that could enhance the development of PPS[28].

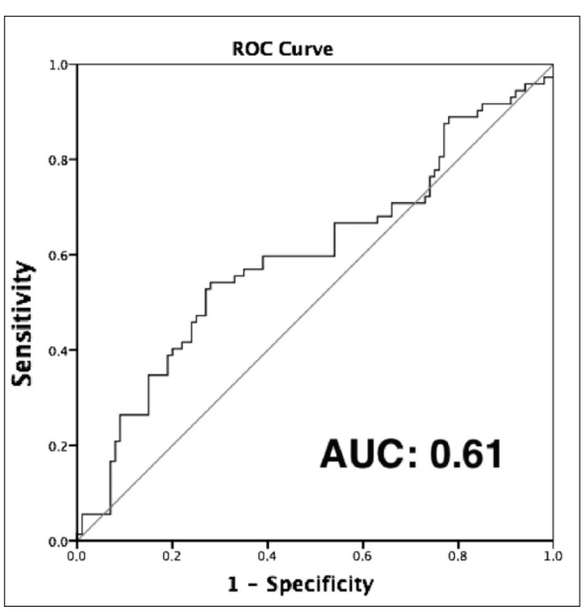

Figure 1. The ROC curve of NLR for prediction of post-pericardiotomy syndrome after cardiac surgery.

We found that the neutrophil count increased significantly in patients with PPS, but no difference in lymphocyte count was detected between patients with and without PPS. An increase in the number of neutrophils may be attributed to the inflammatory condition of PPS. The NLR was higher in patients with PPS compared to those without. Thus, the difference in NLR was due to the difference in neutrophil count between the groups. Previous studies have demonstrated increased serum interleukin (IL)-8 levels in patients with PPS compared to those without[22,23]. IL-8 is a proinflammatory chemokine associated with promoting neutrophil chemotaxis and degranulation in an inflamed environment[29]. Colchicine inhibits the neutrophil chemotactic response to IL-8 and is the only drug proven to be efficacious for preventing PPS[4,30]. These data are consistent with the observation that the neutrophil count is increased in patients with PPS.

Previous studies have revealed that the NLR is increased in certain autoimmune diseases, including ulcerative colitis[16], primary Sjogren's syndrome[17], familial Mediterranean fever[31], psoriasis[32], Behcet's disease[20], systemic lupus erythematosus[21], and rheumatoid arthritis[18].

Only a few studies have examined the role of biomarkers in predicting PPS following cardiac

Surgery. Snefjella And Lappegard[23] screened 50 consecutive patients who underwent postoperative CABG using a panel of inflammatory markers (cytokines, chemokines, growth factors, and complement activation products) and routine laboratory tests. Patients who had developed PPS had higher serum C-reactive protein and IL-8 levels at admission than those who did not. Jaworska-Wilczynska et al[22] also investigated inflammatory markers in patients with PPS and found that the preoperative IL-8 concentration was a risk factor for PPS. They suggested that IL-8 could be useful for diagnosing PPS; however, IL-8 is not measured in every hospital. Therefore, there is a need to develop simple and reliable noninvasive tests to accurately predict the development of PPS in patients undergoing cardiac surgery, even in small hospitals or clinics.

The major criticism of this study is related to the definition of PPS because there is no general agreement on how to diagnose the syndrome. None of the features of this condition are pathognomonic. Secondly, this was a retrospective study.

Conclusions

Our results show that the postoperative NLR may be useful to predict the development of PPS in patients undergoing on-pump CABG. The NLR is a simple, inexpensive, and widely available inflammatory marker that may help predict the development of PPS after CABG in selected patients.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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