

Neutrophil-Lymphocyte Ratio: Prognostic Impact in Heart Surgery. Early Outcomes and Late Survival

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Background. The neutrophil-lymphocyte ratio (NLR) is a recognized marker of inflammation associated with poor outcomes in various clinical situations. We analyzed the prognostic significance of preoperative elevated NLR in patients undergoing cardiac surgery.

Methods. We performed a retrospective review of 3,027 consecutive patients undergoing cardiac surgery. Receiver-operating-characteristic was used to determine the cutoff value for elevated NLR. Multivariate regression was used to determine the predictive value of preoperative NLR on clinical outcomes. Cox proportional hazards functions were used to determine predictors of late events. Late survival data to 16 years was obtained from the Ministry of Interior.

Results. The cutoff value for elevated NLR was 2.6. Patients with elevated NLR were older ($p < 0.0001$), had a higher incidence of cardiac comorbidity ($p < 0.0001$), and higher European System for Cardiac Operative Risk Evaluation score ($p < 0.0001$). An elevated NLR emerged as an independent predictor of operative mortality

(hazard ratio [HR] 2.15, 95% confidence interval [CI]: 1.51 to 3.08, $p < 0.0001$); pleural effusion (HR 1.42, 95% CI: 1.13 to 1.80, $p = 0.003$); low output syndrome (HR 1.54, 95% CI: 1.23 to 1.93, $p = 0.0002$); prolonged ventilation (HR 1.49, 95% CI: 1.23 to 1.82, $p = 0.0001$); or composite outcomes (HR 1.61, 95% CI: 1.36 to 1.91, $p < 0.0001$). The NLR emerged as an independent predictor of late mortality (HR 1.19, 95% CI: 1.11 to 1.28; $p < 0.0001$).

Conclusions. Elevated NLR is associated with a higher incidence of adverse outcomes after cardiac surgery. It is a predictor of operative as well as late mortality. Further studies are warranted to determine whether prophylactic treatment with antiinflammatory agents can prevent such outcomes. It may be warranted to include the baseline NLR as another variable in risk stratification of patients about to undergo cardiac surgery.

(Ann Thorac Surg 2017;■:■-■)

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In recent years, the neutrophil-to-lymphocyte ratio (NLR) has emerged as a sensitive inflammatory marker [1] associated with poor outcomes in a variety of clinical settings. Elevated NLR was found to be associated with adverse outcomes and reduced survival of patients presenting with a wide spectrum of coronary disease, including stable coronary artery disease [2], acute coronary syndrome [3], and myocardial infarction [4, 5]. Elevated NLR was also found to be associated with adverse outcomes and increased mortality among patients undergoing coronary intervention, including both percutaneous coronary intervention and coronary artery bypass graft surgery (CABG) [6-9].

In the present study, we sought to determine the short-term and long-term prognostic significance of elevated NLR in patients undergoing cardiac surgery in our department. The primary endpoint was survival.

Secondary endpoints were low output syndrome, prolonged ventilation, and pleural effusion.

Patients and Methods

Patients

We performed a retrospective review of 4,063 consecutive patients who underwent cardiac surgery utilizing cardiopulmonary bypass between the years 2001 and 2016 and including CABG or valve surgery or mixed surgery. Excluded were patients without preoperative blood count containing absolute values of neutrophils and lymphocytes within 2 weeks before surgery and patients undergoing surgery for active endocarditis, leaving a total of 3,027. Normal values of neutrophils were between 1,400/ μ L and 6,500/ μ L and lymphocytes were between 1,200/ μ L and 3,400/ μ L. Our institutional laboratory participates in the United Kingdom Quality Assurance Scheme quality control program. For the purpose of comparing outcomes, patients with both normal neutrophil count as well as nonelevated NLR at baseline served

Accepted for publication July 17, 2017.

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as the control group. Our Institutional Ethics Review Board approved this study and waived the need for individual patient consent. We compared outcomes between patients with baseline elevated NLR to those of patients with low NLR. Late survival data were obtained from the Ministry of Interior and is 93% complete.

Statistical Analysis

Preoperative, operative, and early postoperative data were collected prospectively in our departmental database (Summit Medical, Europe). The data were imported and analyzed using JMP software (SAS Institute, Cary, NC). The cutoff value for elevated NLR was determined using receiver-operating characteristics. Continuous variables were compared using Student's *t* test and presented as mean $\pm$ SD. Nominal and categorical values were compared using the χ^2 likelihood ratio or Fisher's exact tests. Analysis of variance was used to determine the correlation between values of NLR and operative mortality. Multivariate logistic regression was used to identify predictors of outcomes. Univariate and multivariate Cox proportional hazards functions were used to determine predictors of late events. Variables evaluated as predictors of late events included patient age, preoperative symptoms of congestive heart failure, left ventricle dysfunction, baseline absolute lymphocyte and neutrophil count, baseline NLR, and the European System for Cardiac Operative Risk (EuroSCORE) [10]. Because the EuroSCORE is primarily a predictor of operative mortality, it was not included in the analysis of outcomes other than mortality.

Definitions

Operative mortality was defined as death within 30 days of surgery or within the same hospitalization. Preoperative risk of mortality was calculated using the logistic EuroSCORE. Left ventricular function, degree of mitral regurgitation, and tricuspid regurgitation gradient were determined using transthoracic echocardiograms according to previously established methods [11]. Renal failure was determined if preoperative creatinine level was greater than 1.5 mg%. Acute kidney injury was determined if there was a twofold rise in baseline creatinine or creatinine value of greater than 2 mg/dL in a patient with normal baseline values. Low output syndrome was determined in patients requiring inotropic support, or by clinical assessment if there were indications of malperfusion (low urine output, acidosis, elevated lactate values). Infection includes one or more of the following: deep sternal wound infection, pneumonia, mediastinitis, and septicemia. Urinary tract infection and superficial wound infection were not included in the analysis. Prolonged ventilation was defined as ventilation 24 hours or longer after surgery. Pleural effusion was determined in cases with pleural effusion necessitating pleurocentesis.

Results

Preoperative blood count was available for 3,027 patients (75%), and they comprise the cohort of this study. Preoperative blood count was unavailable for patients who

underwent operation on an urgent basis, as well as patients whose blood tests were not recorded on our institutional database, such as patients from other institutions. The clinical profile of these patients was similar to the study cohort. These patients were therefore not included in our study. The cutoff value for elevated NLR was found to be 2.6. By univariate analysis, patients in the high NLR group had a higher incidence of comorbidity: left ventricular dysfunction ($p < 0.0001$), mitral regurgitation grade ≥ 2 ($p < 0.0001$), and elevated pulmonary pressure ($p < 0.0001$) as well as a higher EuroSCORE ($p < 0.0001$). More cases were performed on an urgent basis ($p < 0.0001$), and there was a higher incidence of postoperative adverse events: low output syndrome ($p < 0.0001$), prolonged ventilation ($p < 0.0001$), pleural effusion ($p < 0.0001$), and operative mortality ($p < 0.0001$). Baseline patient characteristics and operative data are shown in Table 1. Postoperative events are shown in Table 2.

Observed mortality was increased in the elevated NLR group compared with the nonelevated NLR group: 137 of 1,329 (10%) and 54 of 1,698 (3%), respectively ($p < 0.0001$). That was true also in patients with normal baseline neutrophil count ($n = 2,459$). Within this group, mortality

Table 1. Baseline Clinical Variables

Variables	NLR ≥ 2.6	NLR < 2.6	<i>p</i> Value
Number of patients	1,329 (44)	1,698 (56)	...
Male	943 (71)	1142 (67)	0.03
Age, years	66 $\pm$ 11	63 $\pm$ 12	<0.0001
Hypertension	962 (72)	1176 (69)	0.06
Diabetes mellitus	525 (39)	660 (39)	0.7
Chronic lung disease	162 (12)	161 (9)	0.02
Renal failure	251 (19)	130 (8)	<0.0001
Pulmonary hypertension	686 (52)	648 (38)	<0.0001
Stroke	120 (9)	121 (7)	0.05
Peripheral vascular disease	145 (11)	138 (8)	0.009
Atrial fibrillation	242 (18)	202 (12)	<0.0001
Congestive heart failure	771 (58)	824 (49)	0.01
EuroSCORE (logistic)	12 $\pm$ 15	7 $\pm$ 9	<0.0001
Echocardiography			
Left ventricular dysfunction	277 (21)	245 (14)	<0.0001
MR grade ≥ 2	620 (47)	609 (36)	<0.0001
TR gradient	40 $\pm$ 21	34 $\pm$ 14	<0.0001
Operative data			
Pure CABG	479 (36)	813 (48)	<0.0001
CABG + any valve	284 (21)	248 (15)	<0.0001
MV procedure, $\pm$ other	556 (42)	509 (30)	<0.0001
Urgent	348 (26)	336 (20)	<0.0001
Reoperation	139 (10)	94 (5)	<0.0001
Bypass time, minutes	114 $\pm$ 54	103 $\pm$ 50	<0.0001
Ischemic time, minutes	83 $\pm$ 42	76 $\pm$ 37	<0.0001
Need for inotropes	372 (28)	242 (14)	<0.0001

Values are *n* (%) or mean $\pm$ SD.

CABG = coronary artery bypass graft surgery; EuroSCORE = European System for Cardiac Operative Risk Evaluation; MR = mitral regurgitation; MV = mitral valve; NLR = neutrophil-lymphocyte ratio; TR = tricuspid regurgitation.

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