Neutrophil-lymphocyte ratio to predict early stent thrombosis

Índice neutrófilo-linfocitario en la predicción de trombosis temprana del stent

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ABSTRACT

Introduction. Inflammation is the main mechanism proposed in the physiological genesis of stent thrombosis. An expression of the inflammatory state is the lymphocytic neutrophil index. Objective. Evaluate the prognostic value of the lymphococcal neutrophil index in the prediction of early thrombosis of the stent. Method. Prospective research at the Hermanos Ameijeiras Hospital, Havana, Cuba, between December 2018 and June 2019. Results. 196 patients were studied; the variables high levels of neutrophil (p-0.009) and lymphocytic neutrophil index (p-0.007) after the proceeding are significantly related to the presence of stent thrombosis and the ROC curve found a sensitivity of 70% and a specificity of 62% for an index level greater than 6 (0.712; IC95%: 0.610-0.988; 0.012). Conclusion. The increase in the neutrophil-lymphocytic index at 6 hours of percutaneous coronary interventionism has high sensitivity and high specificity as predictive value in early stent thrombosis

Keywords: lymphocytic neutrophil ratio, early stent thrombosis.

RESUMEN

Introducción. La inflamación es el principal mecanismo propuesto en la génesis fisiopatológica de la trombosis del *stent*. Una expresión del estado inflamatorio es el índice neutrófilo linfocitario. Objetivo. Evaluar el valor pronóstico del índice neutrófilo linfocitario en la predicción de trombosis temprana del *stent*. Método. Investigación prospectiva en el Hospital Hermanos Ameijeiras, La Habana, Cuba, entre diciembre de 2018 y junio 2019. Resultados. Se estudiaron 196 pacientes; las variables niveles elevados de neutrófilo (p=0,009) e índice neutrófilo linfocitario (p=0,007) después del proceder se relacionan significativamente con la presencia de trombosis del *stent* y la curva ROC encontró una sensibilidad de 70% y una especificidad de 62% para un nivel del índice mayor de 6 (0,712; IC95%: 0,610-0,988; p=0,012). Conclusión. El aumento del índice neutrófilo-linfocitario a las 6 horas del intervencionismo coronario percutáneo, tiene alta sensibilidad y alta especificidad en la predicción de trombosis temprana del *stent*.

Palabras clave: índice neutrófilo linfocitario, trombosis temprana del stent.

INTRODUCTION

Stent thrombosis (ST) is one of the main complications of percutaneous coronary intervention (PCI) and is associated with high morbidity and mortality rates[1-3]. It is a complex and multifactor process involving several patient-related factors such as early withdrawal of dual antiplatelet therapy, diabetes mellitus, unstable patient, previous ST, and other; anatomical factors such as the spread of coronary artery disease, thin vessels, ostial lesions, coronary bifurcations, and other; and finally procedure-related factors such as complex bifurcation technique, length of the segment treated, and other.[2]

Back in 2008 the Academic Research Consortium published the clinical practice guidelines on how to classify ST.[4] Depending on when the ST occurs, it is classified as acute, subacute, late, and very late ST. Acute (<24 hours) and subacute ST (from 24 hours to 30 days) are called early stent thrombosis. Probable ST is defined as any inexplicable death within the first 30 days after stent implantation or the presence of ST-segment elevation acute coronary syndrome with topography consistent with the territory of the artery treated. On the other hand, definitive ST requires confirmation through angiography or anatomopathological examination of the presence of a thrombus inside the stent or 5 mm anterior or posterior to it.

The advances made in antiplatelet therapy, the ongoing improvements of stents, and the implantation technique used have reduced the rate of ST to 0.7%. This complication is minor in elective (from 0.3% to 0.5%) compared to urgent procedures (3.4%).[5,6] Stents are endovascular devices that are potentially thrombogenic, a property that basically depends on the electropositive charge of the metal surface that seems to be affected by the composition, configuration, and size of the stent and, consequently, by the vessel protective response. Beyond the stent thrombogenic properties as a metal structure there are different clinical, technical, and procedural factors that play a significant role in the occurrence of acute and/or subacute ST (early ST) after its implantation; however, this is not the case when thrombotic events are considered late, which seems to be directly associated with a complex immediate and delayed vessel response with respect to the presence of the stent (usually pharmacological), the platform, the drug, and the polymer. This response is triggered by incomplete endothelization and neointimal formation, hypersensitivity, endothelial dysfunction (late inflammatory response), and late acquired incomplete stent apposition.[7-9]

The rate of early ST seems a little higher with bare-metal stents compared to drug-eluting stents. It has been suggested that the polymer matrix of drug-eluting stents can reduce acute thrombogenicity. The factors associated with the procedure are the most important ones (stent malapposition and underexpansion, edge dissection), but there are other clinical factors involved such as diabetes mellitus, reduced LVEF, genetic traits, among other, that can trigger the inflammatory state.[10,11]

This inflammatory factor that has been described in late and very late ST is associated with stent implantation and there is evidence that it is associated with inflammatory markers and ST.[12]

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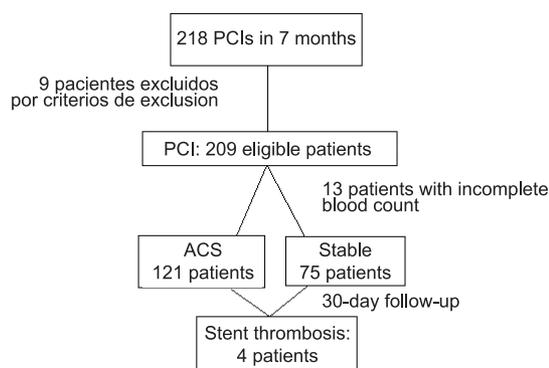
Figure 1. *Fluid balance chart of the study sample.*

The neutrophil-lymphocyte ratio (NLR) is an inflammatory marker associated with the presence, severity, and spread of coronary artery disease,[13] adverse cardiovascular events in patients with acute myocardial infarction previously treated with PCI [14], and with the presence of periprocedural type 4a acute myocardial infarction.[15] This easy-to-determine, reproducible, and cost-effective NLR biomarker is the marker of choice of the inflammatory state. In this sense, there are studies that associate the NLR with ST and the high mortality rate of patients with acute coronary syndrome.[16]

OBJECTIVE

To assess the prognostic value of neutrophil-lymphocyte ratio to predict early stent thrombosis.

METHODOLOGICAL DESIGN

Type of research: applied, descriptive-correlational, and prospective study.
Period and place: Hospital Hermanos Ameijeiras, Havana, Cuba, from December 2018 through June 2019.

PARTICIPANTS

Inclusion criteria
- Patients >18 years undergoing percutaneous coronary intervention.

Exclusion criteria
- Severe left ventricular systolic dysfunction (ejection fraction <30%).
- PCI of chronic total occlusion.
- Myocardial revascularization surgery 3 months before.
- Severe lung disease. Neoplasm. Chronic hematologic disease.
- Corticosteroid therapy within the last year. Chronic inflammatory disease. Active infection when the procedure was performed.

Sample
One hundred and ninety-six consecutive patients who met the inclusion and exclusion criteria during the timeframe mentioned above.

Main variable
- Neutrophil-lymphocyte ratio: it is defined as the absolute number of neutrophils divided by the absolute number of lymphocytes. It was estimated prior to the procedure performed and 6 hours later.
- Stent thrombosis: early ST (probable or definitive) was defined as the ST occurring within the first 30 days after stent implantation.

Techniques and procedures
- Automatic analysis of leukogram: the Pentra-DX NEXUS automated hematology analyzer was used. A fully automated hematology analyzer for the in-vitro diagnosis of anticoagulated whole blood samples with EDTA at 10%.
- Lymphocytes (LYN): expressed as absolute value (#).
- Neutrophils (NEU): expressed as absolute value (#)

Statistics
The comparison of non-parametric values between both groups was conducted using the Mann-Whitney U test. Categorical variables were compared using the chi-square test. Regression analysis was used to assess the predictors of stent thrombosis. Variables with P values <0.05 according to the univariate analysis were included in a multivariate regression model and their odds ratio (OR) was estimated using the 95% confidence interval (95%CI). The ROC curve was established to determine the prediction of the value of NLR in stent thrombosis.

RESULTS

The fluid balance chart of **Figure 1** shows that 218 procedures were performed during the study period. Thirteen out of the 209 eligible patients had incomplete data and 196 patients were studied. Of these, 4 showed early stent thrombosis (2.04%).
Procedural clinical and angiographic variables and laboratory parameters are shown on **Table 1**. The distribution of these variables based on the presence of early stent thrombosis shows that variables such as old age ($P=0.047$), presence of diabetes mellitus ($P=0.04$), bifurcation lesion ($P=0.036$), and acute coronary syndrome ($P=0.04$) are associated with this complication. Similarly, high neutrophil ($P=0.009$) and NLR levels ($P=0.007$) after the procedure are significantly associated with the presence of ST.
The distribution of patients with ST based on the time of appearance, definitive diagnosis, and location is not statistically significant (**Table 2**), which is associated with the poor frequency of stent thrombosis.
The level of NLR based on the presence of ST is shown on **Figure 2** and **Figure 3**. In patients with early stent thrombosis, the NLR was high after the procedure ($P<0.05$), the sensitivity of the ROC curve was 70% and its specificity was 62% for NLR levels > 6 (0.712; 95%CI: 0.610-0.988; $P=0.012$).
In the multivariate analysis only these variables were independently associated with the presence of this complication (**Table 3**): bifurcation lesion (0.905; IC95%: 0.744-0.991; $P=0.003$), postprocedural high neutrophil (0.833; 95%CI: 0.645-0.911; $P=0.012$) and NLR levels (0.809; 95%CI: 0.689-0.873; $P=0.009$).

TABLE 1. Procedural, clinical, angiographic variables and laboratory parameters in the study patient.

Variable	Patients	Presence of early stent thrombosis		P
		Yes (4)	Not (192)	
Age	65.3±9.1	69.6±8.2	63.1±6.1	.047
Male (%)	122 (62.2%)	3 (75%)	119 (61.9%)	.23
DM (%)	83 (42.3%)	4 (100%)	79 (41.1%)	.04
Smoking	92 (46.9%)	2 (50%)	90 (46.9%)	.6
CKD > 1 (%)	31 (15.8%)	1 (25%)	30 (15.6%)	.78
Previous AMI	52 (26.5%)	2 (50%)	50 (26.0%)	.09
LVEF	55.4±3	46±8.9	57±4.2	.056
UA/NSTEMI	121(38.2%)	3 (75%)	118 (61.5%)	.04
ASA + clopidogrel	196 (100%)	4 (100%)	192 (100%)	1
Statins	133 (67.9%)	4 (100%)	129 (67.2%)	.12
SYNTAX score	24.1±4.2	28.2±4.1	23. 0±3.3	.23
Bifurcation lesion (%)	71 (36.2%)	4 (100%)	67 (34.9%)	.036
Total length of the stented segment (mm)	21±9.2	28±10.1	20±8.3	.38
Presence of thrombus	12 (6.12%)	1 (25%)	11 (5.7%)	.09
Stent thrombosis related artery - LMCA - LAD - Diagonal - Cx - RCA	18 (9.2%) 88 (44.9%) 6 (3.1%) 29 (14.8%) 79 (40.3%)	1 (25%) 2 (50%) 1 (25%) 0 0	17 (8.9%) 86 (44.8%) 5 (2.6%) 29 (15.1%) 79 (41.1%)	.9 .45 .2
Complex bifurcation technique	4 (2%)	0	4 (2.1%)	
Conventional stent	109 (55.6%)	1 (25%)	108 (56.3%)	.6
Drug-eluting stent	87 (44.4%)	3 (75%)	84 (43.8%)	.5
Neutrophils (×10³/mm³) - Preprocedural - Postprocedural	 3.0±1.2 3.8±1.8	 3.4±0.5 5.8±0.4	 3.0±1.1 3.7±1.2	 .08 .009
Lymphocytes (×10³/m³) - Preprocedural - Postprocedural	 1.9±1.3 1.4±1.2	 1.9±1.4 0.9±0.4	 2.0±1.0 1.9±1.2	 .08 .14
NLR - Preprocedural - Postprocedural	 2.1±1.5 2.7±1.8	 3.5±1.3 6.5±0.3	 2.8±1.9 3.0±1.0	 .09 .007

AMI, acute myocardial infarction; ASA, acetylsalicylic; CKD, chronic kidney disease; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; NLR, neutrophil-lymphocyte ratio; NSTEMI, non-ST-elevation acute myocardial infarction; UA, unstable angina.

TABLE 2. Distribution of patients with early stent thrombosis according to time and location.

|	Acute ST	Subacute ST	Definitive ST	Probable ST	LMCA	LAD	Diag
Case#1	X		X			X	
Case#2		X	X			X	
Case#3		X	X				X
Case#4		X		X	X		

ST, stent thrombosis.

DISCUSSION

Inflammation is the main mechanism proposed in the pathophysiological process of stent thrombosis.[12] The neutrophil-lymphocyte ratio expresses the inflammatory state of coronary arteries. High neutrophil levels increase the secretion of inflammatory markers like the proteolytic enzyme elastase that deteriorates the vascular basement membrane causing endothelial damage.[17] In contrast, the lymphocyte levels associated with the secretion of cortisol go down worsening the inflammatory response.[18]

TABLE 3. Multivariate analysis of variables associated with the presence of stent thrombosis.

Variables	OR (95%CI)	P
Age	1.023 (0.874-2.064)	.147
Diabetes mellitus	0.994 (0.836-1.582)	.245
UA/NSTEMI	1.693 (0.726-2.059)	.133
Bifurcation lesion	0.905 (0.744-0.991)	.003
Postprocedural neutrophil levels (6 hours)	0.833 (0.645-0.911)	.012
Preprocedural NLR levels	1.19 (0.428-1.977)	.544
Postprocedural NLR levels (6 hours)	0.809 (0.689-0.873)	.009

95%CI, 95% confidence interval; NSTEMI, non-ST-elevation acute myocardial infarction; OR, odds ratio; ST, stent thrombosis; UA, unstable angina.
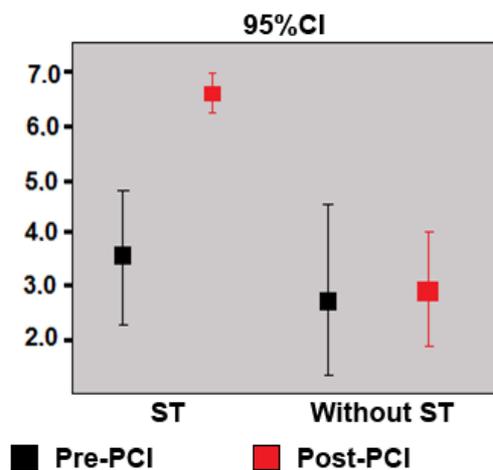
Figure 2. *Association between the NLR and the presence (or not) of ST.*
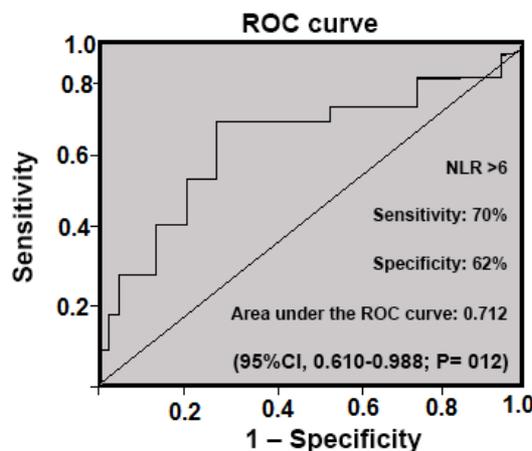
Figure 3. *ROC curve. Neutrophil-lymphocyte ration to predict ST.*

Our data suggest that there is a significant correlation between higher postprocedural NLR levels > 6 and the presence of early stent thrombosis with high sensitivity and specificity. Burak A et al.[16] found similar results. They showed that NLRs > 4.9 have high sensitivity and specificity to predict in-hospital mortality while keeping a close correlation with the presence of ST.

The neutrophil count 6 hours after the procedure was independently associated with the presence of stent thrombosis in this series. Former studies correlate this parameter with the higher cardiovascular mortality due to coronary artery disease,[19] which explains the inflammatory state found in the coronary tree of patients with ST.

STUDY LIMITATIONS

The size of this study was not big enough. Although the percentage of patients with early stent thrombosis is similar to that reported by the medical literature, these patients were misrepresented in this study.

CONCLUSION

High neutrophil-lymphocyte ratio levels 6 hours after a percutaneous coronary intervention show high sensitivity and specificity to predict early stent thrombosis.

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