

Neutrophil-to-lymphocyte ratio: A useful tool for interventional cardiology

Suilbert Rodríguez Blanco[✉] , MD; Ángel G. Obregón Santos , MD, PhD; Abel Y. Leyva Quert , MD; and Ángela R. Gutiérrez Rojas , MD

Department of Interventional Cardiology, *Hospital Clínico-Quirúrgico Hermanos Ameijeiras*. Havana, Cuba.

Este artículo también está disponible en español

ARTICLE INFORMATION

Received: February 13, 2019
Accepted: April 18, 2019

Competing interests

The author declares no competing interests

Abbreviations

AMI: acute myocardial infarction
MDM: myocardial damage markers
NLR: neutrophil-to-lymphocyte ratio
PCI: percutaneous coronary intervention
PMI: peri-procedure myocardial infarction

ABSTRACT

Cardiovascular diseases are the main cause of morbidity and mortality worldwide, and in Cuba, they have increased in recent years. Their ischemic origin represents the most frequent isolated disease causing death in Cuban people. The percutaneous coronary intervention (PCI) –as part of their treatment– is among the most developed areas within current Cardiology. There is a growing role of inflammation in these diseases; therefore, the search for new inflammatory markers, that are related to this procedure, is crucial. The neutrophil-to-lymphocyte ratio has been associated with the occurrence of complications during the PCI and monitoring of these patients, thus, an update in this regard is proposed. The evidence shows a significant relationship between the increase of this ratio, with the appearance of peri-procedure myocardial infarction, as well as with the adverse results in the follow-up; in a way, that opens a new route of research in interventional cardiology.

Keywords: Cardiovascular diseases, Percutaneous coronary intervention, Neutrophil-to-lymphocyte ratio

Índice neutrófilo-linfocitario: Una herramienta útil en la cardiología Intervencionista

RESUMEN

Las enfermedades cardiovasculares son la principal causa de morbilidad y mortalidad en el mundo, y en Cuba han mostrado un incremento en los últimos años. Su causa isquémica constituye la enfermedad aislada más frecuente de muerte en los cubanos, y el intervencionismo coronario percutáneo (ICP) –como parte de su tratamiento– se encuentra entre las áreas de mayor desarrollo dentro de la Cardiología actualmente. Existe un papel creciente de la inflamación en estas enfermedades, por lo que se impone la búsqueda de nuevos marcadores inflamatorios que tengan relación con este procedimiento. El índice neutrófilo-linfocitario se ha relacionado con la aparición de complicaciones durante el ICP y el seguimiento de estos pacientes, por lo que se propone una actualización al respecto. La evidencia muestra una relación significativa entre el aumento de este índice con la aparición de infarto de miocardio peri-procedimiento, así como con los resultados adversos en el seguimiento; de manera que abre una nueva puerta de investigación en la cardiología intervencionista.

Palabras clave: Enfermedades cardiovasculares, Intervencionismo coronario percutáneo, Índice neutrófilo-linfocitario

✉ S Rodríguez Blanco
Hospital Hermanos Ameijeiras
San Lázaro 701, e/ Belascoaín y
Marqués González. Centro Habana
10300. La Habana, Cuba.
E-mail address:
suilbertr@infomed.sld.cu

INTRODUCTION

Cardiovascular diseases remain the leading cause of morbidity and mortality worldwide¹. According to data from the American Heart Society, more than 2200 Americans die each day as a result of these diseases, about one death every 40 seconds, with a third of these before the age of 75 years¹.

In Cuba, heart diseases are the leading cause of death. In 2017 they caused 27176 deaths, with an increase of 6918 deaths in relation to the year 2000. Among these, the ischemic origin caused 17628 deaths, 1278 more than in 2016². In this way, the ischemic cardiac disease is the most common isolated cause of death in Cuba.

Percutaneous coronary intervention (PCI) is among the most developed areas in current Cardiology, which enabled the progressive incursion in increasingly complex scenarios, as bifurcation lesions, thin vessels, very calcified lesions, angled lesions, and located in the left main coronary artery, chronic total occlusions and others, which increases the risk of complications such as myocardial damage, ranging from injury to peri-procedure myocardial infarction (PMI). Cardiac troponins are the golden standard on the determination of this myocardial damage.

Several studies have shown the important role that inflammation plays in cardiovascular diseases and, within these, in the progression and destabilization of the atherosclerotic lesion^{3,4}. Many have been the inflammatory markers proposed in this scenario and, recently, the white blood cell count has generated special interest in the scientific community, because it has shown an association with the increase in cardiovascular risk factors, in addition to the benefits of using a simple, inexpensive and easily reproducible inflammatory marker⁵.

Recently, the neutrophil-to-lymphocyte ratio (NLR) that, besides these characteristics, is routinely used and is widely available in all Cuban centers, has proven to be an important inflammatory marker and a potential predictor of cardiovascular risk^{6,7}. In this regard, it has been found a strong association between increased NLR and adverse cardiovascular events –including mortality in patients with acute myocardial infarction (AMI)– and the adverse clinical outcomes in patients who underwent an elective PCI⁸⁻¹⁰. For this reason, we have decided to carry out this review with the aim of deepening into these important aspects that are related to the increase of the NLR.

NEUTROPHIL-TO-LYMPHOCYTE RATIO AND PERI-PROCEDURE MYOCARDIAL INFARCTION

The incidence of PMI is very variable, from 2.6% to 30%, depending on the diagnostic criteria used, as well as the local practice^{11,12}. The presence of this complication of the PCI has implications for prognosis, therefore, to detect it and stratify it is essential for guiding therapy in these patients.

The PMI may result from peri-operative recognizable events, alone or in combination, as: coronary dissection, occlusion of a major coronary artery or a side branch, alteration of collateral circulation, slow flow or absence of reperfusion, distal embolization and microvascular obstruction. Such events induce inflammation of myocardial cells that surround the necrosis¹³. The occurrence of myocardial cell damage with necrosis related to the procedure can be diagnosed when the elevation of myocardial damage markers (MDM) are detected at 3-6 hours of the PCI, compared to values previous to the procedure, which establishes the definition of PMI or AMI type 4a^{14,15}. In previous studies, increased numbers of cardiac biomarkers after the procedure, especially CK-MB, were associated with a poor clinical outcome¹⁴⁻¹⁷.

In a meta-analysis of 22353 patients, Feldman *et al*¹⁶ reported 45% increase in the incidence of all-cause mortality after a mean of 17.7 months, in patients with increased levels of cardiac troponins after the PCI, and they found no association between high levels of MDM after PCI with an increase of the relative risk of death. In this context, the NLR, emerging inflammation marker, could have a value in predicting and diagnosing the myocardial damage secondary to PCI, and could be used as a probable MDM.

This NLR shows a balance between the overall content of neutrophils and blood lymphocytes. In the case of a myocardial damage, neutrophils are the first leukocytes found in the area of a damaged myocardium, with the local secretion of procoagulant substances and increase of proteolytic and oxidative effect¹⁸. Furthermore, the lymphocytopenia is commonly encountered in response to stress and increasing corticosteroid levels¹⁹. In this way, the increase in the quotient between the absolute values of neutrophils and lymphocytes –which is called NLR–, is a greater exponent of the inflammatory state and surpasses the separate analysis of each of them.

Neutrophils' infiltration into the damaged myo-

cardium contributes to the phenomenon of coronary “no-reflow” (no reperfusion), with increased blood viscosity and hypercoagulability. As part of the inflammatory reaction, cytokines facilitate activation of the extrinsic pathway of the coagulation cascade²⁰ and, additionally, the distal embolization of leukocytes and aggregates of leukocytes and platelets contributes to decreased perfusion in the microcirculation²¹.

In the world bibliography, NLR has been linked to peri-procedure myocardial damage of PCI. Bressi *et al*¹⁸ demonstrated that the increase in NLR, in the first 24 hours of this intervention, is proportional to the post-procedure myocardial damage. In this observational study of over 500 patients, a 6.6% had PMI, where a significant increase in the NLR was observed at 6 hours of the PCI in relation to the basal level (5.750 [4.360-9.095] vs. 4.370 [3.370-5.950]; $p < 0.001$) and also at 24 hours (5.180 [4.440-8.065] vs. 4.670 [3.920-5,710]; $p = 0.003$); with a strong correlation between NLR and MDM: CK-MB (Spearman's $\rho = 0.377$; $p = 0.031$) and troponins (Spearman's $\rho = 0.506$; $p = 0.003$).

The NLR also plays an important role in the prediction of the PMI. The PCI in complex lesions increases the risk of this complication and a variable that relates to the complex coronary anatomy is the SYNTAX score greater than 32. In this regard, the NLR has been linked to the presence of greater load of coronary artery disease; thus, Kaya *et al*²², in their research, found among predictors of a SYNTAX score > 32 NLR = 4.4 ± 1.2 (OR [odds ratio] 1.67; CI 95%: 1.25-2.24; $p < 0.001$), with an area under the ROC curve of 0.72 (0.65-0.80; $p < 0.001$), where the optimal cut-off value for the NLR was 2.7 with a sensitivity of 72% and specificity of 61%. More recently, the relationship between NLR and severity of the coronary disease was also demonstrated when using the Gensini score ($r = 0.413$; $p = 0.001$)²³.

NEUTROPHIL-TO-LYMPHOCYTE RATIO AND LONG-TERM OUTCOMES OF PATIENTS TREATED WITH PCI

The success of the PCI includes the angiographic aspect, that of the procedure and clinical success, which is evaluated in monitoring these patients. Good clinical results, short and long terms, are the desired objective in monitoring patients treated with PCI and evaluated according to endpoints as: nonfatal AMI, the need for redo coronary revasculariza-

tion, major bleeding and mortality.

The stratification of the complications' risk, in the follow-up of patients treated with this technique, is essential for the planning of rehabilitation and secondary prevention strategies, hence, the search of biochemical markers related to results in the follow-up is imperative for interventional cardiology. The relationship existing between elevated levels of troponin immediately after PCI with poor clinical outcomes in the management of these patients is well known²⁴. In a meta-analysis, including 20 studies, was evaluated the connection between troponins' levels after the PCI and mortality, and it showed a significant relationship between increasing these MDM and mortality, with a mean follow-up of 16.5 months (OR 1.35; CI 95%: 1.13-1.60)⁶.

Inflammation plays a role in the progression, magnitude and destabilization of the atherosclerotic disease, pathophysiological basis of coronary artery disease^{3,4}. The rupture of an atheroma plaque is a mediated phenomenon, among other factors, for a complex inflammatory process where neutrophils and lymphocytes interact as immune and adaptive responses respectively, modulating the inflammatory response at different stages of the atherothrombotic process.

There is a growing interest in the association between NLR and the risk of cardiovascular events after PCI^{8,25,26}. This ratio adds to the long list of inflammatory markers proposed and it has been used as an independent predictor of poor prognosis in monitoring patients with stable coronary artery disease and as a predictor of mortality, in the short and long terms, in patients with acute coronary syndrome. The usefulness of NLR as a risk marker in this disease has already been proved. Its increase has been related with a higher severity of coronary artery disease in a cohort of 3005 patients, who were performed coronary angiography, where a NLR higher than 3 was associated with more obstructive coronary artery lesions (OR 2.45; $p < 0.001$) and a worse prognosis, frequently, of multivessel coronary artery disease (HR [hazard ratio] 1.55; $p = 0.01$) at 3 years of follow-up²⁰.

Recently, a meta-analysis of ten studies²⁵ showed the significant association between increased NLR and increased risk of all-cause mortality and adverse cardiovascular events. The possible pathophysiological explanation for this relationship is based on the role of neutrophils in mediating the inflammatory process generated by myocardial damage⁸; lymphocytes are related to the regulatory pathway of the

immune system and it has been shown that the inflammatory process leads to lymphocyte apoptosis^{23, 27}. Therefore, a compound inflammation marker, reflecting increased neutrophils with decreased lymphocytes, can provide additional information in the assessment of cardiovascular risk. Tamhane *et al*⁴ evaluated the role of the NLR in the long-term outcome of patients with ST-segment elevation AMI, treated with PCI, and found that the increased NLR at the time of diagnosis related significantly with all the cause of hospital deaths (OR 2.04; p=0.013) and at 6 months (OR 3.88; p<0.001). Other studies have linked the high levels of NLR with clinical restenosis of patients treated with PCI (OR 1.85, p<0.001)²⁸ and with cardiovascular mortality²⁶.

FINAL CONSIDERATIONS

In the hemodynamic and interventional cardiology units of Cuba, the performance of coronary procedures in more complex clinical and anatomical settings is increasing, which implies an increased risk of myocardial damage and motivates the search for new markers that are related to percutaneous coronary intervention. Therefore, the relationship of the neutrophil-to-lymphocyte ratio with the prediction and diagnosis of complications during the procedure, and the prediction of adverse events in the follow-up, open a new route in interventional cardiology.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, *et al*. Heart Disease and Stroke Statistics – 2016 Update: A Report From the American Heart Association. *Circulation*. 2016; 133(4):e38-360.
2. Ministerio de Salud Pública. Anuario Estadístico de Salud 2017. La Habana: Dirección Nacional de Registros Médicos y Estadísticas de Salud; 2018.
3. Poludasu S, Cavusoglu E, Khan W, Marmur JD. Neutrophil to lymphocyte ratio as a predictor of long-term mortality in African Americans undergoing percutaneous coronary intervention. *Clin Cardiol*. 2009;32(12):E6-E10.
4. Tamhane UU, Aneja S, Montgomery D, Rogers EK, Eagle KA, Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. *Am J Cardiol*. 2008;102(6):653-7.
5. Park JJ, Jang HJ, Oh IY, Yoon CH, Suh JW, Cho YS, *et al*. Prognostic value of neutrophil to lymphocyte ratio in patients presenting with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol*. 2013;111(5):636-42.
6. Han YC, Yang TH, Kim DI, Jin HY, Chung SR, Seo JS, *et al*. Neutrophil to Lymphocyte Ratio Predicts Long-Term Clinical Outcomes in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. *Korean Circ J*. 2013;43(2):93-9.
7. Herrmann J. Peri-procedural myocardial injury: 2005 update. *Eur Heart J*. 2005;26(23):2493-519.
8. Califf RM, Abdelmeguid AE, Kuntz RE, Popma JJ, Davidson CJ, Cohen EA, *et al*. Myonecrosis after revascularization procedures. *J Am Coll Cardiol*. 1998;31(2):241-51.
9. White HD. The prequel: defining prognostically important criteria in the periprocedural PCI troponin saga. *Circ Cardiovasc Interv*. 2012;5(2):142-5.
10. Jaffe AS, Apple FS, Lindahl B, Mueller C, Katus HA. Why all the struggle about CK-MB and PCI? *Eur Heart J*. 2012;33(9):1046-8.
11. Prasad A, Stone GW, Stuckey TD, Costantini CO, Mehran R, Garcia E, *et al*. Relation between leucocyte count, myonecrosis, myocardial perfusion, and outcomes following primary angioplasty. *Am J Cardiol*. 2007;99(8):1067-71.
12. Fowler AJ, Agha RA. Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography – the growing versatility of NLR. *Atherosclerosis*. 2013;228(1):44-5.
13. Damman P, Wallentin L, Fox KA, Windhausen F, Hirsch A, Clayton T, *et al*. Long-term cardiovascular mortality after procedure-related or spontaneous myocardial infarction in patients with non-ST-segment elevation acute coronary syndrome: a collaborative analysis of individual patient data from the FRISC II, ICTUS, and RITA-3 trials (FIR). *Circulation*. 2012;125(4):568-76.
14. Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, *et al*. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol*. 2013;62(17):1563-70.
15. Liou K, Jepson N, Kellar P, Ng B, Isbister J, Giles

- R, *et al.* Prognostic significance of peri-procedural myocardial infarction in the era of high sensitivity troponin: A validation of the Joint ACCF/AHA/ESC/WHF Universal Definition of Type 4a Myocardial Infarction with high sensitivity troponin T. *Heart Lung Circ.* 2015;24(7):673-81.
16. Feldman DN, Kim L, Rene AG, Minutello RM, Bergman G, Wong SC. Prognostic value of cardiac troponin-I or troponin-T elevation following non-emergent percutaneous coronary intervention: a meta-analysis. *Catheter Cardiovasc Interv.* 2011; 77(7):1020-30.
 17. Arbel Y, Finkelstein A, Halkin A, Birati EY, Revivo M, Zuzut M, *et al.* Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography. *Atherosclerosis.* 2012;225(2):456-60.
 18. Bressi E, Mangiacapra F, Ricottini E, Cavallari I, Colaiori I, Di Gioia G, *et al.* Relation of neutrophil to lymphocyte ratio with periprocedural myocardial damage in patients undergoing elective percutaneous coronary intervention. *Am J Cardiol.* 2016;118(7):980-4.
 19. Stevens LA, Coresh J, Feldman HI, Greene T, Lash JP, Nelson RG, *et al.* Evaluation of the modification of diet in renal disease study equation in a large diverse population. *J Am Soc Nephrol.* 2007;18(10):2749-57.
 20. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, *et al.* Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet.* 2013;381(9867):629-38.
 21. Ellis SG, Guetta V, Miller D, Whitlow PL, Topol EJ. Relation between lesion characteristics and risk with percutaneous intervention in the stent and glycoprotein IIb/IIIa era: An analysis of results from 10,907 lesions and proposal for new classification scheme. *Circulation.* 1999;100(19):1971-6.
 22. Kaya A, Kurt M, Tanboga IH, Işık T, Günaydın ZY, Kaya Y, *et al.* Relation of neutrophil to lymphocyte ratio with the presence and severity of stable coronary artery disease. *Clin Appl Thromb Hemost.* 2014;20(5):473-7.
 23. Jagadish HR, Divyaprakash M, Manjunath R, Girish PG. Association between neutrophil to lymphocyte ratio and severity of coronary artery disease. *Int J Adv Med.* 2018;5(2):265-70.
 24. Nienhuis MB, Ottervanger JP, Bilo HJ, Dikkeschei BD, Zijlstra F. Prognostic value of troponin after elective percutaneous coronary intervention: A meta-analysis. *Catheter Cardiovasc Interv.* 2008; 71(3):318-24.
 25. Wang X, Zhang G, Jiang X, Zhu H, Lu Z, Xu L. Neutrophil to lymphocyte ratio in relation to risk of all-cause mortality and cardiovascular events among patients undergoing angiography or cardiac revascularization: a meta-analysis of observational studies. *Atherosclerosis.* 2014;234(1):206-13.
 26. Gibson PH, Croal BL, Cuthbertson BH, Small GR, Ifezulike AI, Gibson G, *et al.* Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. *Am Heart J.* 2007; 154(5):995-1002.
 27. Azab B, Zaher M, Weiserbs KF, Torbey E, Lacossiere K, Gaddam S, *et al.* Usefulness of neutrophil to lymphocyte ratio in predicting short- and long-term mortality after non-ST-elevation myocardial infarction. *Am J Cardiol.* 2010;106(4):470-6.
 28. Turak O, Ozcan F, Isleyen A, Tok D, Sokmen E, Buyukkaya E, *et al.* Usefulness of the neutrophil-to-lymphocyte ratio to predict bare-metal stent restenosis. *Am J Cardiol.* 2012;110(10):1405-10.