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REVIEW

The role of inflammation in cardiovascular diseases: the predictive value of neutrophil–lymphocyte ratio as a marker in peripheral arterial disease

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Abstract: Peripheral arterial disease (PAD) is an important manifestation of atherosclerosis, with increasing prevalence worldwide. A growing body of evidence shows that the systemic inflammatory response is closely related to the development, progression, and prognosis of atherosclerosis. In the last decade, several studies have suggested the role of measured inflammatory biomarkers as predictors of severity and prognosis in PAD in an effort to stratify the risk of these patients, to improve treatment selection, and to predict the results after interventions. A simple inflammatory marker, more available than any other, is the neutrophil–lymphocyte ratio (NLR), which can be easily obtained in clinical practice, based on the absolute count of neutrophils and lymphocytes from the differential leukocytes count. Many researchers evaluated vigorously the NLR as a potential prognostic biomarker predicting pathological and survival outcomes in patients with atherosclerosis. In this work, we aim to present the role of NLR as a prognostic marker in patients with PAD through a thorough review of the literature.

Keywords: neutrophil–lymphocyte ratio, peripheral arterial disease, inflammation, cardiovascular diseases, biomarkers

Introduction

Peripheral arterial disease (PAD) is an important manifestation of atherosclerosis, which affects >202 million people worldwide,[1] and is associated with cardiovascular events,[2] with increased all-cause and cardiovascular mortality.[3,4] PAD, despite the advances registered in its treatment, still has a worse prognosis compared with coronary artery disease (CAD)[5] by various factors, including the high rate of in-stent restenosis, which occurs with an important contribution of the inflammatory response.[6,7] These negative outcomes have brought in sight the need of biomarkers as predictors of outcomes to ensure better risk stratification, proper selection of treatment approaches, and, if necessary, additional multitarget approaches (such as the endovascular brachytherapy).[8]

In recent years, the literature has highlighted the value of systemic inflammation as an important element in the development, progression, and prognosis of atherosclerosis.[9,10] It is worth to mention that PAD is the atherosclerotic manifestation that shows the greater relationship with systemic inflammation.[11] Several inflammatory markers have been shown to be useful in clinical studies on risk stratification and prognosis of patients with PAD,[12,13] as well as in those with disease in other vascular beds as cerebral and coronary.[14–16]

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Among the inflammatory markers, neutrophil–lymphocyte ratio (NLR), defined as the ratio of absolute counts of neutrophils and lymphocytes, has gained space as an effective biomarker in the stratification and prognosis of atherosclerotic cardiovascular disease (CVD), and in particular PAD.[17] The NLR is a derived marker, simple, relatively inexpensive, more available than any other, and has shown itself to be a good predictor for other multiple cardiovascular outcomes[18–20] that reflect an imbalance in the inflammatory cells and the role of activated neutrophils in atherogenesis.[21,22] In a representative sample from the National Health and Nutrition Examination Survey, including 9,427 subjects, the average NLR was 2.15 in the general population, being significantly higher in subjects who reported diabetes, CVD, and smoking than in those who did not.[23]

In this article, we reviewed the clinical studies that evaluated the role of inflammatory biomarkers as predictors of outcomes in patients with PAD, with particular emphasis on NLR.

Prognostic value of inflammatory biomarkers in CVDs in general

Multiple inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) have been associated with cardiovascular events.[15,24,25] CRP is associated with CAD, ischemic stroke, and mortality by vascular and nonvascular causes.[15,26]

The NLR as a biomarker in CAD

On CAD, a high NLR is associated with severity of disease, as was evident in a cohort of 3,005 patients undergoing coronary angiography for several indications, in which those with NLR >3 had more advanced obstructive CAD (odds ratio [OR] 2.45, $P<0.001$) and worse prognosis, with higher rates of major cardiovascular events (hazard ratio [HR] 1.55, $P=0.01$) within 3 years of follow-up.[27] NLR is a predictor of mortality in patients with ischemic heart disease both in stable CAD[19] and in acute coronary syndrome.[20,28,29] A high NLR at admission for acute coronary syndrome is associated with all-cause in-hospital (OR 2.04, $P=0.013$) and 6-month mortality (OR 3.88, $P<0.001$).[18] In treated patients, a high pre-intervention NLR was an independent predictor of in-stent restenosis after percutaneous coronary intervention (OR 1.85, $P<0.001$),[30] saphenous vein graft failure for those undergoing coronary artery bypass grafting,[31] and cardiovascular mortality.[32] In a meta-analysis of eight cohort studies with patients undergoing myocardial revascularization or coronarography, a high NLR increased about twice the risk of cardiovascular and all-cause mortality.[33]

The NLR as a biomarker in cerebrovascular disease

In patients with stroke, the NLR is an independent mortality predictor in the short and long term.[34–36] An NLR ≥5.9 at admission was associated with significant functional dependence (OR 6.72, $P=0.025$) and predicted mortality at 90 days (OR 6.69, $P=0.006$) after adjusting for potential confounders.[37] In those patients with ischemic stroke who underwent carotid ultrasonography, NLR significantly predicted the degree of carotid stenosis in male patients.[37] In a study in Turkey with patients who presented to the emergency service with cerebrovascular accident (stroke and transient ischemic attack), the NLR was significantly higher in patients who died ($P<0.001$) and in those with ischemic or hemorrhagic stroke than in those with transient ischemic attack ($P<0.001$).[38]

The NLR as a biomarker in other vascular diseases

The role of NLR seems to begin even before the occurrence of any target organ damage, as was demonstrated in a cohort in which a higher NLR level significantly correlated with an increased risk of developing hypertension compared to participants with lower levels (OR 1.23; 95% confidence interval [CI] 1.06, 1.43).[39] In other studies in hypertension, patients with nondipper pattern (that is associated with cardiovascular mortality) presented significantly higher mean NLR than those with dipper pattern (3.1±0.95 vs 1.8±0.52, $P<0.001$).[40] NLR is also associated with resistant hypertension[41] and other risk factors for atherosclerosis such as metabolic syndrome[42] and diabetes.[43] Table 1 summarizes the clinical studies on the predictive value of inflammatory biomarkers in cardiovascular outcomes.

Inflammatory markers in PAD

Several studies have demonstrated the association between inflammatory markers and the incidence, severity, response to treatment, and prognosis of PAD.[44–47] CRP was, in a cohort, the strongest nonlipidic predictor of PAD (relative risk [RR] 2.8 for the highest quartile in comparison to the lowest).[44] In other studies, the CRP was a significant predictor of major adverse limb events (target vessel revascularization, amputation, or disease progression) and major cardiovascular events in patients with PAD who have undergone angioplasty or stent[47] and a predictor of mortality.[12,48]

In patients being treated with statins for PAD, the benefit of reducing mortality from all causes and CVD was only significant in those with baseline CRP above the median and not in those with baseline CRP below the median

Table 1 Clinical studies on the predictive value of inflammatory biomarkers in various cardiovascular outcomes other than PAD

Study	Year	Marker	Patients and/or type of CVE	Threshold	Assessment period	Results
Chia et al[79]	2009	Total leukocyte and neutrophil counts	STEMI	Leukocyte: >10,800/mm^3 and neutrophil: >8,000/mm^3	24 hours before and 1 day, 2 days, 3 days, 5 days, and 30 days after PCI	Elevated leukocyte and neutrophil counts after primary PCI were directly related to myocardial infarct size, decreased LVEF, and independently predicted cardiovascular outcomes.
Ridker et al[24]	2000	hs-CRP, IL-6, and others	28,263 apparently healthy postmenopausal women	hs-CRP: 0.85 mg/dL; IL-6: 2.7 pg/mL	At baseline	In multivariate analyses, hs-CRP was the only inflammatory marker that independently predicted the risk of CVE. Patients in the highest hs-CRP quartiles had significantly higher risk compared to those in the lowest.
Hong et al[80]	2006	hs-CRP	Patients with angiographically significant coronary artery stenosis	0.5 mg/dL	Before stent implantation	In patients with soft plaque, an elevated hs-CRP level was significantly associated with ISR.
Papa et al[19]	2008	NLR	Patients with stable angiographically documented CAD	Multiple cutoffs (≤1.62, 1.63–2.5, and >2.55)	At baseline	The highest NLR tertile was an independent predictor of cardiac mortality in patients with stable CAD.
Arbel et al[27]	2012	NLR	Patients undergoing coronary angiography for various indications	Multiple cutoffs (<2, 2–3, and >3)	At the time of coronary angiography procedure	A high NLR value (>3) was an independent predictor of CAD severity and predictor of worse clinical outcome.
Arbel et al[29]	2014	NLR	STEMI	6.5	At the time of coronary angiography procedure	A higher NLR (≥6.5) was independently associated with lower ejection fraction and higher mortality rates up to 5 years.
Azab et al[28]	2010	NLR	NSTEMI	Multiple cutoffs (<3, 3–4.7, and >4.7)	At admission	A high NLR (>4.7) was an independent predictor of short- and long-term mortality.
Wang et al[35]	2016	NLR	ICH	7.35	At admission and next morning	A higher NLR (≥7.35) was associated with increased mortality in patients with ICH.
Misumida et al[81]	2015	NLR	NSTEMI	2.8	At admission	A higher NLR (≥2.8) was an independent predictor of LM/3VD in patients with NSTEMI.
Belen et al[41]	2015	NLR	Resistant hypertension	Multiple cutoffs (1.87, 2.11, and 3.15)	During data collection	Patients with resistant hypertension had significantly higher NLR (3.15) than those with controlled hypertension or normotensives.
Duffy et al[82]	2006	NLR	Patients undergoing PCI	Multiple cutoffs (1.7, 3.2, and 11.2)	Before the procedure	Patients in higher tertiles of NLR (11.2) had increased risk of long-term mortality, regardless the reason of the PCI indication.
Núñez et al[83]	2008	NLR	STEMI	Multiple cutoffs (quintiles)	At admission and daily for the first 96 hours	Patients in higher quintiles of NLR (fourth and fifth) presented the highest mortality risk.
Kaya et al[84]	2013	NLR	STEMI	Multiple cutoffs (<2.3, 2.3–4.4, and >4.4)	At admission	A higher tertile of NLR (>2.3) was an independent predictor of both in-hospital and long-term thrombosis, nonfatal myocardial infarction, and cardiovascular mortality.
Tokgoz et al[85]	2013	NLR	Acute stroke	5	At admission	NLR >5.0 was a predictor of short-term mortality in acute stroke patients.
Tokgoz et al[34]	2014	NLR	AIS	4.81	At admission	NLR (>4.81) at the time of hospital admission was a predictor of short-term mortality, independent of the volume of infarct.

(*Continued*)

Table 1 (*Continued*)

Study	Year	Marker	Patients and/or type of CVE	Threshold	Assessment period	Results
Hyun et al[37]	2015	NLR	Patients with acute to subacute ischemic stroke	Mean comparison between groups according to carotid IMT	At admission	Mean NLR was significantly higher among male patients with high carotid IMT compared to those with low IMT (3.9 vs 2.65).
Ertaş et al[86]	2013	NLR	Patients with nonvalvar atrial fibrillation	Mean comparison among subjects with or without stroke	At admission	Mean NLR was significantly higher among subjects with stroke compared to those without (5.6 vs 3.1).
Brooks et al[36]	2014	NLR	AIS	5.9	At admission	A higher NLR (≥5.9) predicted poor outcome and death at 90 days after endovascular stroke therapy.
Taşoğlu et al[31]	2014	NLR	Patients undergoing CABG surgery	Multiple cutoffs (1.69, 2.55, and 3.80)	Preprocedural	A high preoperative NLR was an independent predictor of saphenous vein graft failure in those undergoing CABG.
Balli et al[87]	2015	NLR	Patients who underwent PCI for bifurcation lesions	3.43	Before and after PCI intervention	A high NLR (>3.43) was an independent predictor of ISR in patients who underwent bifurcation PCI.
Cho et al[88]	2015	NLR	Angina and NSTEMI	2.6	Before PCI	A high NLR (>2.6) was an independent predictor of long-term adverse clinical outcomes such as all-cause mortality, cardiac death, and myocardial infarction.
Park et al[89]	2013	NLR	STEMI	Multiple cutoffs (1.4, 1.5–1.9, 2.0–2.4, and ≥2.5)	After 12 hours fast	A higher NLR (≥2.5) was independently associated with arterial stiffness and CCS.
Shah et al[17]	2014	NLR	Asymptomatic, apparently healthy individuals, from NHANES-III	Multiple cutoffs (<1.5, 1.5–<3, 3–4.5, and >4.5)	At NHANES-III data collection time	A high NLR (>4.5) was an independent predictor of CHD mortality and improved marginally the Framingham risk score in prediction of CHD mortality.

Abbreviations: AIS, acute ischemic stroke; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, coronary calcium score; CHD, coronary heart disease; CVE, cardiovascular events; hs-CRP, high-sensitive C-reactive protein; ICH, intracerebral hemorrhage; IL-6, interleukin-6; IMT, intima–media thickening; ISR, in-stent restenosis; LM/3VD, left main and/or three-vessel disease; LVEF, left ventricular ejection fraction; NHANES-III, National Health and Nutrition Examination Survey-III; NLR, neutrophil–lymphocyte ratio; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

(HR 0.44; 95% CI 0.23–0.88 vs HR 0.73; 95% CI 0.31–1.75).[13] This result suggests that the benefit of statin is closely related to their anti-inflammatory effect, which is in accordance with the findings in patients with CAD, in which the benefit of statins in survival occurs mainly in subjects with high initial CRP, with fall during treatment, independent of lipid level.[49,50] It has also been evident in the finding that statin mitigated plaque inflammation, measured by noninvasive imaging with 18F-fluorodeoxyglucose positron emission tomography.[51,52] And, even in apparently healthy individuals, with elevated baseline high-sensitive CRP, treatment with statin reduced significantly the incidence of major cardiovascular events.[53]

Another inflammatory marker associated with PAD and its progression is the IL-6.[46,54] In a cohort of 12 years of follow-up, IL-6 was the inflammatory marker that showed the strongest and consistent predictive value for progression of PAD.[54] And, in patients with established PAD, persistently high IL-6 levels are associated with faster functional decline[25] and greater severity of disease with critical limb ischemia (CLI).[46] Table 2 summarizes the clinical studies on the predictive value of general inflammatory biomarkers (other than NLR) in PAD.

The particular role of NLR as a prognostic marker in PAD

PAD severity

In PAD, a high NLR is associated with increased severity of disease,[55,56] as was evident in a retrospective cohort of 2,121 patients with PAD in which CLI occurred significantly more in the group with a high NLR (48.5% vs 24.3%, $P<0.001$).[56] In another study including 1,995 patients with PAD, the increase in NLR was associated with a significant increase in CLI rates (20.4%, 26.1%, and 36.1% for the first, second, and third tertiles, respectively).[55]

Response to treatment and prognosis

In patients who initially received conservative therapy for CLI, a high NLR was an independent predictive factor for amputation and was associated with lower amputation-free survival.[57,58] A high NLR was a risk factor for amputation within 30 days in patients who underwent initial embolectomy for acute limb ischemia[31] and an independent predictor of graft failure (occlusion or ipsilateral amputation) in those undergoing infrainguinal bypass grafting.[59]

Mortality

A high NLR not only predicts disease severity and response to treatment but also is a predictor of mortality.[60] In patients followed for PAD, a high NLR predicted independently long-term cardiovascular mortality (HR 2.04, $P=0.004$).[60] A high NLR at admission for chronic CLI is associated with increased mortality.[61]

In treated patients, a high pre-intervention NLR was an independent predictor of mortality in those who have undergone infrapopliteal percutaneous intervention for CLI (HR 1.95, $P<0.03$).[62] And, even in those undergoing elective revascularization, a high preoperative NLR was independently associated with increased mortality.[63,64] Table 3 summarizes the clinical studies that have assessed the role of NLR as a prognostic biomarker in PAD.

Potential mechanism underlying NLR role in PAD and atherosclerosis in general

Despite substantial epidemiological evidence of the predictive role of NLR in atherosclerotic manifestations, there is a lack of pathophysiological body for such findings. This derived marker is an imbalance of inflammatory cells (disproportionate dominance of neutrophils over lymphocytes), and it may be a reflection of a deeper imbalance in the immunologic response, with the dominance of effectors cells over the regulatory cells, mainly $CD4^+$ T-helper cells.[65,66] Some studies have described the domain of subtype T-helper 17 over the regulatory T-cells, resulting in the activation of the interleukin-17 axis that is in turn associated with vascular dysfunction, progression of atherosclerosis, and vascular events.[65,67,68] Several other mechanisms may be involved in the link between NLR and atherosclerosis, including endothelial dysfunction[69,70] and oxidative stress.[71] However, in light of the current literature, there are no sufficient data to support the formulation of a conceptual or pathophysiologic model linking the two. Despite this gap, we know that atherosclerosis is mainly an inflammatory disease,[72] and currently effective therapies, particularly statins, are associated with decreasing inflammatory response.[49,51,52,73] The most accurate understanding of the mechanisms underlying this emerging evidence from clinical studies should be a substrate of a call to action for future studies in basic science, translational, experimental, and clinical levels.

Concerns and limitations of the NLR as a cardiovascular biomarker

Some concerns arise regarding the potential use of NLR as a cardiovascular biomarker. NLR is increased in other situations such as nonalcoholic fatty liver disease, metabolic syndrome, psoriasis, and cancer.[42,74,75] All these conditions share in common an inflammatory or immune response in a given point of their pathogenesis, and interestingly, most of these have been also associated with CVDs as described

Table 2 Clinical studies on the predictive value of inflammatory biomarkers (other than NLR) in PAD

Study	Year	Marker	Number of patients	Threshold	Assessment period	Results
Tzoulaki et al[54]	2005	CRP, IL-6, and ICAM-1	1,592 subjects	Multiple cutoffs in tertiles	At baseline, 5 years, and 12 years	Higher plasma levels of CRP were associated with increasing severity of PAD, and CRP, IL-6, and ICAM-1 were associated with atherosclerosis and its progression.
Haumer et al[90]	2005	Total neutrophils count	398 patients	Multiple cutoffs in tertiles	At baseline	Patients with neutrophil counts in upper tertile exhibited an increased risk for all MACE, death, and the composite of myocardial infarction, stroke, and death, compared to those in the lower tertiles.
Beckman et al[91]	2005	CRP	110 patients	Mean comparison between subjects with or without PAD	At baseline	CRP was significantly higher in subjects who had PAD (3.83 vs 2.11). Patients with both decreasing ABI and increasing CRP had the highest risk for hard events (myocardial infarction, stroke, and death).
Bleda et al[92]	2013	hs-CRP	143 patients (85 diabetic and 58 nondiabetic) who underwent EVT	Mean comparison (11.8 vs 4.3 mg/L)	Before the procedure	High basal hs-CRP, but not diabetes, was associated with incidence of reintervention and mortality during post EVT follow-up period.
Stone et al[47]	2014	hs-CRP	118 patients who underwent elective angioplasty or stent placement	0.8 mg/dL	Before the intervention	Elevated preprocedural hs-CRP (>0.80) was a predictor of MALE and MACE by 2 years.
Bleda et al[93]	2015	CRP	121 patients undergoing EVT	9.8 mg/dL	Before the procedure	High baseline CRP (>9.8) increased risk of EVT failure and the necessity of reintervention at first year.
Owens et al[94]	2007	hs-CRP	Patients undergoing lower extremity bypass	5 mg/L	On the morning of lower extremity bypass	Elevated hs-CRP (>5 mg/L) was correlated with CLI at presentation and adverse postoperative graft-related or cardiovascular events.
De Haro et al[95]	2009	CRP	330 patients diagnosed with PAD	Median comparison among three clinical severity groups	At the study data collection time	The clinical severity of PAD increased significantly with higher plasma CRP levels (median 3.8, 8.33, and 12.83 mg/L for mild, moderate, and severe disease, respectively).
Hoegh et al[96]	2008	hs-CRP	452 patients with symptomatic PAD	10 mg/L	At study baseline	The baseline level of hs-CRP was significantly higher among those who developed primary end point (death or amputation) and those who developed an overall secondary end point (lower limb thrombosis, myocardial infarction, or stroke).
Lin et al[97]	2010	CRP	85 diabetic patients with PAD and infected foot ulcers who underwent PTA	50 mg/L	Before PTA	Higher level of CRP was associated with major amputation after initial PTA.
McDermott et al[98]	2006	hs-CRP	487 subjects (296 with and 191 without PAD)	NA (continuous)	At baseline and annually for 3 years	Greater annual increases in hs-CRP were predictors of greater functional decline during the subsequent year in patients with PAD and may reflect functional decline during the past year in subjects without PAD.
Shankar et al[99]	2007	CRP	1,611 subjects without traditional risk factors for PAD (CVD, diabetes, and hypertension)	Multiple cutoffs (quartiles)	At the study data collection time	The prevalence of PAD was higher among subjects in the highest CRP quartiles compared to those in the lowest (OR 6.38, *P* 0.005). This association persisted even after subgroup analysis by sex, age, education, smoking, and body mass index.
Vainas et al[100]	2005	hs-CRP	387 patients with PAD	Multiple cutoffs (tertiles)	During baseline assessment	Higher hs-CRP tertiles at baseline were significantly associated with decreased ABPI at baseline and at 12 months, reflecting severity. Furthermore, serum hs-CRP was associated with death and/or any cardiovascular event during a median 24-month follow-up period.

Abbreviations: ABI, ankle–brachial index; ABPI, ankle–brachial pressure index; CLI, critical limb ischemia; CRP, C-reactive protein; CVD, cardiovascular disease; EVT, endovascular therapy; hs-CRP, high-sensitive C-reactive protein; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; MACE, major adverse cardiovascular events (stroke, myocardial infarction, or death); MALE, major adverse limb events (femoropopliteal interventions); NA, not applicable; NLR, neutrophil–lymphocyte ratio; OR, odds ratio; PAD, peripheral arterial disease; PTA, percutaneous transluminal angioplasty.

Table 3 Clinical studies on the role of NLR as prognostic biomarkers in PAD

Study	Year	Number of patients	Threshold	Assessment period	Results
Taşoğlu et al[101]	2014	254	5.2	At admission	A higher NLR (≥5.2) was a risk factor for amputation within 30 days after surgery in patients who underwent embolectomy for acute limb ischemia.
Kullar et al[59]	2012	126	NA	Postoperative	A higher NLR was an independent predictor of graft failure (occlusion or ipsilateral amputation) after infrainguinal bypass grafting.
Belaj et al[55]	2015	1,995	2.5	At the study data collection time	Increased rate of CLI was observed with increasing NLR tertiles (20.4%, 26.1%, and 36.1% for the lowest, second, and third tertiles, respectively).
Spark et al[61]	2010	149	5.25	At admission	A higher NLR (≥5.25) was independently associated with shorter survival in patients being treated for CLI.
Erturk et al[60]	2014	593	3	At the study data collection time	A higher NLR (>3) was found to predict independently long-term cardiovascular mortality in patients with intermittent claudication and CLI.
González-Fajardo et al[63]	2014	561	5	At admission	A higher NLR (>5) was associated with higher 5-year mortality and lower AFS in patients with chronic CLI who underwent elective infrainguinal open or endovascular revascularization.
Taşoğlu et al[58]	2014	104	3.2	At admission	A higher NLR (≥3.2) was a good predictor of lower overall limb survival in patients with nonreconstructable CLI.
Chan et al[62]	2014	83	5.25	Before the procedure	Patients with a higher NLR (≥5.25) had an increased risk of death after infrapopliteal percutaneous angioplasty.
Bhutta et al[64]	2011	1,021	5	Before the surgery	A high preoperative NLR (>5) was independently associated with mortality (OR 2.21) within 2 years after elective major vascular surgery.
Gary et al[56]	2013	2,121	3.95	At admission	In patients with PAOD, an increased NLR (>3.95) was significantly associated with CLI and other vascular end points (myocardial infarction and stroke).
Luo et al[57]	2015	172	3.8	Posttreatment	A higher NLR (≥3.8), the posttreatment NLR, was identified as an independent predictive factor for amputation in patients who receive at first conservative therapy.

Abbreviations: AFS, amputation-free survival; CLI, critical limb ischemia; NA, not applicable; NLR, neutrophil–lymphocyte ratio; OR, odds ratio; PAD, peripheral arterial disease; PAOD, peripheral arterial occlusive disease.

by Ganzetti et al[76] in his recent review. Despite being a nonspecific marker, NLR has shown consistency in predicting outcomes in atherosclerotic diseases,[16–19,23,33–36,58–60] and even in the nationally representative sample of American subjects, NLR was significantly higher in those who reported diabetes, CVD, and smoking than in subjects who did not.[23] In addition, NLR has a good correlation with other inflammatory markers such as CRP,[77] presenting even better performance as a biomarker in specific conditions.[78]

There are some important limitations of this study. The first is the use of different cutoff values in different studies and the scarcity of published works validating the normality value in the general population. However, as we just underlined, most studies in atherosclerosis found a higher cutoff than the average NLR value (2.15) found in the only existing study in the general population,[23] which suggests the plausibility of the association found in those studies. The second is the absence of studies that have validated the normality value for specific populations. This point is critical because as a derived ratio, it is, of course, affected by changes either in the numerator or the denominator. For example, subjects who have a relative constitutional lymphopenia would easily be classified as having a high NLR, without necessarily an increased inflammatory activity. So, it is prone to potential bias that could lead to false-positive associations. The third is relative to the paucity of studies clarifying the mechanisms underlying the association between NLR and atherosclerosis.

Conclusion and future directions

From the available evidence, it is very likely that the presence of a high NLR has predictive value for future vascular events in asymptomatic and symptomatic subjects. This simple, fast, and widely available biomarker can offer an additional noninvasive tool for risk stratification to assess the severity, response to treatment and prognosis of PAD.

More studies are necessary to know and clarify the role of NLR as an additional tool in PAD. This is reinforced because its role has been reproducible and consistent in other vascular beds as cerebral and coronary, especially in the current scenario of growing recognition of various diseases, with chronic inflammatory component as risk factors for atherosclerosis.

Further studies should be addressed to establish the normality value for specific populations to clarify the underlying mechanisms in atherogenesis and should be designed to

assess the effectiveness of anti-inflammatory therapies using the fall of NLR as a surrogate outcome and assess its role to guide therapy.

Disclosure

The authors report no conflicts of interest in this work.

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