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Neutrophil-to-Lymphocyte Ratio is a strong predictor of atherosclerotic carotid plaques in older adults

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Abstract *Background and aims:* The Neutrophil-to-Lymphocyte Ratio (NLR), an index of systemic inflammation, has been reported to be associated with subclinical atherosclerosis, but its predictive role of the presence of carotid atherosclerotic plaques remains undefined. This study aims to assess this association which gives additional value to this biomarker, with respect to the main risk factors, in the prediction of carotid atherosclerosis in older adults.
Methods and results: We recruited 324 patients, aged ≥65 years, without hematopoietic disorders, and/or history of malignancies, evidence of acute infections, chronic inflammatory status, and history of glucocorticoid therapy within the past three months, hospitalized in the Unit of Internal Medicine, University of Catania, Catania, Italy from January 2014 to December 2016. All patients underwent blood sampling for white blood cell, neutrophil, lymphocyte and platelet counts, and for measurements of inflammatory markers, NLR was calculated as the ratio of the absolute neutrophil count to the absolute lymphocyte count. Patients also underwent carotid scan by ultrasonography (US) to evaluate abnormalities of carotid wall. NLR resulted a strong predictor of the presence of carotid plaques. NLR > 2.4 predicted with 80% probability carotid plaques ($p < 0.01$), while NLR > 3.68 gave 97% probability ($p = 0.013$). Furthermore, NLR > 2.4 was associated with an average presence of 2.86 carotid plaques ($p < 0.001$). Fibrinogen and CRP performed well, but with lesser significance, as predictors of the presence of carotid plaques ($p = 0.002$).
Conclusion: NLR is a strong predictor of the presence and the number of carotid atherosclerotic plaques. Its use could be useful to identify the risk of harboring carotid plaques.

Introduction

Cardiovascular disease is the leading cause of morbidity, disability and hospitalization, particularly in older adults [1]. Previous reports have underscored that inflammation plays a key role in the development and progression of atherosclerosis [2,3]. In fact, inflammatory cells contribute to atherosclerotic lesion initiation and disruption, leading in turn to acute coronary syndrome and other cardiovascular events, as a consequence of atherosclerotic plaque instability or rupture [4,5]. Carotid intima-media thickness (cIMT), a well established marker of subclinical atherosclerosis, is a risk factor for cardiovascular disease and can

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be used to predict cardiovascular events [6]. Some inflammatory markers (CRP and fibrinogen), but not all, are measured in routine clinical practice to estimate the probability of the presence of atherosclerotic lesions. In this regard, mounting evidence has shown that white blood cell (WBC) and WBC subtypes count are reliable markers of inflammation [7]. Specifically, the Neutrophil-to-Lymphocyte Ratio (NLR), a fast and simple method for assessing inflammatory status calculated as the ratio of absolute neutrophil count to absolute lymphocyte count, has been recently investigated as a new predictor for cardiovascular risk [8]. To date, NLR provides information about the inflammatory state [9], encompassing the effects of neutrophil elevation, secondary to acute inflammation, together with lymphocyte depletion, secondary to stress-induced redistribution of lymphocytes to lymphatic organs, as well as lymphocyte apoptosis [10]. As a matter of fact, lymphopenia was shown to develop secondary to stress-related cortisol release in patients with myocardial infarction [11]. In this regard, a close relationship between an altered NLR and a worsening in prognosis of cardiovascular, metabolic and inflammatory diseases was also shown [12–15]. The objective of this study was therefore to evaluate the relationship between NLR and carotid atherosclerotic plaques, evaluated by carotid artery ultrasonography.

Methods

Study population

This prospective study included 324 older adults (aged $\geq$ 65 years) who were consecutively admitted to the Department of Internal Medicine, Cannizzaro Hospital, Catania, Italy, from January 2014 to December 2016. Patients with hematopoietic disorders, history of malignancies and/or treatment with chemotherapy, evidence of acute infections, chronic inflammatory status, history of glucocorticoid therapy within the past three months and with secondary hypertension were not included in the study.

Hypertension was defined when blood pressure was $\geq$140/90 mmHg or if patients were taking anti-hypertensive drugs. Dyslipidemia was defined if patients showed cholesterol levels above the range provided by the NCEP ATP III Guidelines (National Cholesterol Education Program Adult Treatment Panel III Guidelines) [16], or were taking lipid lowering drugs. Diabetes mellitus was defined in presence of a fasting plasma glucose >126 mg/dL on two consecutive readings, or history of diabetes mellitus, or the use of anti-diabetic medications. Patients were asked whether they were current smokers or formerly smokers.

Fasting blood samples, were drawn from a large antecubital vein in each patient and collected in EDTA tubes, for measurements of white blood cell, neutrophil, lymphocyte and platelet count at the time of admission, using a Coulter LH 750 Haematology Analyzer (Beckman Coulter, Milan, Italy). NLR was calculated as the ratio of the absolute neutrophil count to the absolute lymphocyte count. Inflammatory markers, serum creatinine, fibrinogen and ferritin were assayed by an automated analyzer (Immulite analyzer, Medical System SPA, Genoa, Italy); Erythrocyte Sedimentation Rate (ESR) was determined by VES-Matic Cube 80 Analyzer (Diesse Diagnostica Senese SPA, Italy), using tubes with EDTA as anticoagulant. C-reactive protein (CRP) was measured using an automated latex-enhanced turbidimetric immunoassay (Unicel DxC 600i, Beckman Coulter, Milan, Italy). Glomerular filtration rate was calculated using CDK-EPI (Chronic Kidney Disease Collaboration) formula [17]; chronic kidney disease was categorize using K-DOQI (Kidney Disease Outcomes Quality Initiative) classification [18]. Participants rested in the supine position for 15 min prior to carotid US examination. Bilateral common carotid arteries (CCA), carotid bifurcations, internal carotid and external carotid arteries in longitudinal and transverse planes were scanned using a 3.5–10 MHz linear multi-frequency transducer (Esaote MyLab 30 Gold). Intima media thickness (IMT) was estimated in longitudinal plane, in a region free of atherosclerotic plaques of the common carotid artery far wall, at 0.5, 1, and 1.5 cm from the carotid bifurcation, taking for analysis the average of the three measurements. An increased IMT was defined as $\geq$0.9 mm in one or both carotid arteries. The presence of atherosclerotic plaque was identified in transverse plan and defined as a focal structure that encroached into the arterial lumen by at least 0.5 mm, or 50% of the surrounding IMT value, or in presence of thickening $\geq$1.5 mm as measured from the media–adventitial interface to the intima–lumen interface [19]. Carotid artery atherosclerosis was defined in presence of increased IMT $>$ 0.9 mm or of plaque (IMT $\geq$ 1.5 mm) [20]. The number of plaques was calculated considering not contiguous sites. Patients' characteristics, clinical features laboratory and echographic data were collected and gathered in an electronic database. This study was carried out in accordance with the Declaration of Helsinki. All participants signed a written consent form. The experimental protocols and the process for obtaining informed consent were approved by the appropriate institutional review committee.

Statistical analysis

A preliminary estimation of the minimum sample size to obtain a power of 80% at a significance level of 0.05 was done. Assuming an effect size of 0.5, a minimum sample size of 64 patients in either group (presence vs absence of carotid atherosclerosis) was necessary. Continuous data are expressed as mean $\pm$ SD, while categorical data as frequencies and percentages. Proportions were compared by chi-square test with Yates' correction for continuity or Fisher's exact test, as appropriate; comparison of continuous variables was performed by Student's t-test. Receiver operating characteristic (ROC) curves were constructed to evaluate the sensitivity and specificity of hypertension, diabetes, dyslipidemia, smoking and NLR to predict the presence of carotid atherosclerotic plaques. A P value $\leq$ 0.05 was considered statistically significant. Risk models have been developed by using logistic-regression

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