



## Original article

# The predictive value of elevated neutrophil to lymphocyte ratio for long-term cardiovascular mortality in peripheral arterial occlusive disease



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## ABSTRACT

**Background:** Peripheral arterial occlusive disease (PAOD), which is common in male gender and elderly population, is related with increased cardiovascular mortality and morbidity. Neutrophil to lymphocyte ratio (NLR) has been found to be an independent predictor of cardiovascular mortality in atherosclerosis. The aim of the present study was to investigate the association between NLR and cardiovascular mortality both in patients with intermittent claudication and critical limb ischemia.

**Methods:** In a retrospective study, 593 consecutive patients who had been admitted to the inpatient ward of the vascular department of a large tertiary training and research hospital with diagnosis of symptomatic PAOD between May 2009 and September 2012 were included. Patients were divided into two groups according to their NLR as follows: high NLR (NLR > 3.0) and low NLR (NLR ≤ 3.0) groups.

**Results:** During the course of the present study [median follow-up period of 20 months (interquartile range, 12–27)], 75 deaths occurred out of 508 patients (14.8%). Cardiovascular mortality was found to be significantly higher in elevated NLR group ( $n=43$ ) as compared to low NLR group ( $n=32$ ) (23.6% vs 9.8%, respectively;  $p < 0.001$ ). Even after adjustment of various risk factors, NLR > 3 and age were found as independent predictors of long-term cardiovascular mortality in Cox regression analysis [hazard ratios (95% confidence interval), 2.04 (1.26–3.30) and 1.04 (1.01–1.07),  $p=0.004$  and  $p=0.004$ , respectively].

**Conclusion:** We demonstrated that an increased NLR was related with higher cardiovascular mortality in patients with PAOD, who were admitted with critical limb ischemia or intermittent claudication. NLR, which reflects the patient's inflammatory status, is an inexpensive and readily available biomarker that provides an additional level of risk stratification beyond that provided by conventional risk scores in predicting long-term cardiovascular mortality in PAOD.

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## Introduction

Peripheral arterial occlusive disease (PAOD), which is common in male gender and elderly population, is related with increased cardiovascular mortality and morbidity [1]. Because of the economic, social, and health burden impact, early and precise detection

of PAOD is crucial for both general and high-risk populations [2]. Many observational studies have presented a white blood cell (WBC) count as a predictor of coronary artery disease (acute myocardial infarction), stroke, and cardiovascular mortality and morbidity that is independently related with several coronary risk factors [3–6].

Leukocytes, which are of monocyte–macrophage lineage, play an important role in development of atherosclerosis and its complications by mediating several biochemical pathways such as arachidonic acid metabolites and platelet aggregating factors. Also, increased WBC count can be used to stratify the patients into risk categories for future major cardiovascular events after acute

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myocardial infarction [7,8]. Neutrophil to lymphocyte ratio (NLR) is an inexpensive and readily available indicator, which reflects the severity and extension of systemic inflammation and atherosclerosis [9]. NLR has been found to be an independent predictor of short-term mortality in patients with acute coronary syndrome [10–12]. Also, the relation of elevated NLR with higher mortality and morbidity in patients with severe PAOD including critical limb ischemia has been shown in recent studies [13]. The strong independent predictive effect of high NLR on survival was reported in patients undergoing high-risk vascular surgery such as abdominal aortic aneurysm repair, lower limb revascularization, coronary artery bypass graft, and carotid endarterectomy in a large observational study [14].

Although the relation between NLR and cardiovascular mortality had been shown in critical limb ischemia, there is no information about this association in patients with intermittent claudication in the literature. The aim of the present study was to investigate the relation between NLR and cardiovascular mortality both in patients with intermittent claudication and critical limb ischemia.

## Materials and methods

### Study design and patient selection

In this retrospective study, 593 consecutive patients who had been admitted to an inpatient ward of the vascular department of a large tertiary training and research hospital with diagnosis of symptomatic PAOD between May 2009 and September 2012 were included. The PAOD defined as >50% stenosis in the symptomatic lower limb, which was assessed by means of clinical evaluation and confirmed by lower limb angiography performed according to current state of the art protocols. Symptomatic PAOD was also defined as intermittent claudication at rest and critical limb ischemia, which included rest pain, ulceration, and gangrene [15]. Fontaine classification was applied for categorization of PAOD. Patients were divided into two groups according to their NLR as follows: high NLR (NLR > 3.0) and low NLR (NLR ≤ 3.0) groups. Patients with a history of surgical lower limb amputation as a consequence of PAOD, previous surgical or endovascular lower limb revascularization, history of autoimmune disease, acute infections unrelated PAOD, recent (<3 months) coronary or peripheral revascularization, recent (<3 months) acute coronary syndrome or stroke, decompensated heart failure, malignancy, hepatic or renal disease, chronic inflammatory disease, and leukocyte count above reference limits ( $\geq 12 \times 10^9/L$ ) were excluded from the study.

Demographic information, cardiovascular risk factors, and comorbidities (age, smoking habits, hyperlipidemia, body mass index, hypertension, diabetes mellitus, coronary artery disease, history of myocardial infarction or stroke, and current medication), physical examination and interventional (vascular surgery, angioplasty, stenting) data were recorded by systematic review of patient hospital files. Also, the results of complete series of routine laboratory investigations including complete blood cell count and levels of 12 h overnight fasting low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, and triglyceride were recorded. On admission, venous blood samples were obtained from all the patients and WBC, neutrophils, and lymphocyte counts were measured as part of the automated complete blood count using a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland, Inc., Mervue, Galway, Ireland). NLR was calculated as the ratio of the neutrophils and lymphocytes both obtained from the same automated blood sample at admission in the present study.

Firstly, the study population was divided into three groups based on their admission NLR in order to determine the association of

NLR on mortality and morbidity in patients with PAOD as follows: high (NLR > 3.0), intermediate (NLR 2.0–3.0), and low (NLR < 2.0) (Fig. 1). Because of the insignificant relation between mid and low NLR groups in terms of cardiovascular mortality in Kaplan Meier survival plot, both the intermediate and low NLR groups were combined. The final patient categories were presented as follows: high NLR group (NLR > 3.0) and low NLR group (NLR ≤ 3.0).

### Definitions

Smokers included current and former smokers. Hypertension was diagnosed if systolic arterial pressure exceeded 140 mmHg and/or diastolic arterial pressure exceeded 90 mmHg, or if the patient used antihypertensive drugs. Diabetes mellitus (DM) was diagnosed if plasma fasting glucose exceeded 126 mg/dL or if the patient used hypoglycemic agents. Hyperlipidemia was defined as fasting total serum cholesterol > 200 mg/dL, LDL cholesterol > 130 mg/dL, or serum triglycerides > 180 mg/dL, or if the patient used lipid-lowering drugs because of a history of hypercholesterolemia [16]. Renal failure was defined as a glomerular filtration rate < 60 mL/min per 1.73 m<sup>2</sup>, which was estimated by the simplified modification of diet in renal disease equation [17].

### Study endpoints

Follow-up data were obtained from hospital records or by telephone interview with patients, their relatives, or their family physicians. The clinical end point of the present study was cardiovascular mortality. Cardiovascular death was defined as unexplained sudden death, death due to myocardial infarction, decompensated heart failure, or hemodynamically significant arrhythmia.

The study was approved by the local review board and ethics committee, and all patients gave their written informed consent.

### Statistical analysis

Continuous data are presented as the median and the interquartile range (IQR, range from the 25th to the 75th percentile). Discrete data were given as counts and percentages. The chi-square test was used to compare for categorical variables and Mann–Whitney

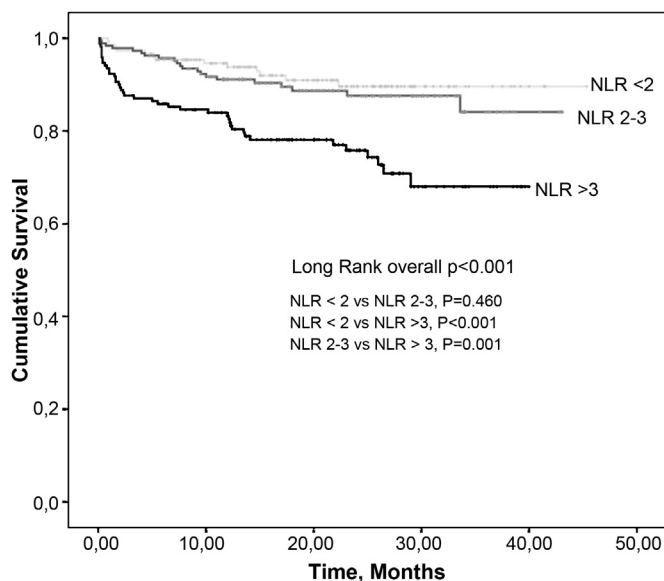


Fig. 1. Kaplan–Meier curve for long-term survival according to neutrophil to lymphocyte ratio (NLR) groups. Cumulative event-free survival defined as freedom from death.

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