Cardiovascular Risk

Subjects: Cardiac & Cardiovascular Systems

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Cardiovascular disease (CVD) is the leading cause of death in women, although traditionally, it has been considered as a male dominated disease. Chronic inflammation plays a crucial role in the development of insulin resistance, diabetes type 2 and CVD.

Keywords: women ; gender ; medicine ; cardiovascular risk ; menopausal transition ; meta inflammation ; bio-mediators

1. Leukocyte Counts and Ratios as Markers of Inflammation in Cardiovascular Disease

Low grade inflammation has been implicated in the development of DM2, CVD and other common aging diseases [1]. This has led to various inflammatory markers being studied extensively, for prognostic purposes, in the context of aging diseases and mortality. The most commonly used inflammatory markers were IL-6 and C-reactive protein (CRP) [2]. This early trend has now changed to the more prevalent assessment of the total white blood cell count (WBC) and specific leukocyte classes, as being less expensive and more easily accessible markers of inflammation. The total WBC count comprises several cell types, including granulocytes (mainly neutrophils), monocytes and lymphocytes. When monocytes enter the circulation and come to tissue, they serve as precursors of macrophages or dendritic cells (DCs) [3].

Inflammation is associated with increased recruitment of inflammatory and immune cells from the circulation to the tissue via dysfunctional vascular endothelial cells [4]. Monocytes/macrophages and T-lymphocytes are cell types that are prevalent in atherosclerotic plaque. Growing evidence indicates also the role of neutrophils in both, the development and the progression of atherosclerotic lesions, and plaque destabilization and rupture. Emerging evidence indicates the critical role of neutrophils in CV risk factor-related target-organ disease [5]. This role of neutrophils is associated with their increased recruitment from the circulation by dysfunctional endothelium and prolonged persistence in tissue, due to decreased apoptosis and disturbed clearance by macrophages [4][6].

The role of lymphocytes is to mount specific (adaptive) immunity [7]. The evolution of the specific immune reaction begins with antigen presentation by DCs to naive T helper (CD4+) lymphocytes. Through the process of proliferation and differentiation of specific T cell clones, there is a parallel process of effector functions polarization, towards either a predominantly humoral, T helper 2 (Th2)-mediated, or cellular, Th1-mediated immune response, depending on which cytokines are dominant in the micro-environment. A key mechanism that protects tissue against prolonged immune reactions or immune reactions to self-antigens, is the active suppression of effector T cell functions by regulatory T cells (Treg) [8]. In conditions associated with tissue damage or hypoxia, there can be a non-resolving inflammation and/or auto-immune reactions, by redirecting the immune reaction towards the dominance of the Th1/Th17 effector pathway [9].

The total WBC has been recognized as being associated with CVD and predictive of specific CV and overall mortality [10]. However, many factors have been found to contribute to variations in this parameter, for example, age, sex, smoking, clinical markers of obesity and insulin resistance, which places limitations on its use as a predictive marker in CVD [10]. Similar limitations on the prognostic value of major types of circulating leukocytes, have also been described. In order to account for interactions between different leukocyte types in predicting mortality and other outcomes, which suggests that particular leukocyte types play different roles in the pathophysiology process, leukocyte subtype-based ratios, such as neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio, or platelet-to-lymphocyte ratio, have recently begun to be used as prognostic factors in patients with cancer or CVD, or to predict specific and all-cause mortality in the general population [11].

The left side—cell-mediated (Th1 type) immunity is the key immune mechanism in atherosclerosis. Participating cells include macrophages, NK (natural killer) cells, dendritic cells, CD4+ Th_1 (T-helper, type 1), T-lymphocytes, and CD8+ (cytotoxic) T-lymphocytes. The immune reaction is initiated by the interaction of toll-like receptors (TLR), exposed on the surface of dendritic cells, with antigens. Activated dendritic cells release the cytokine IL-12, which together with the cytokine interferon-gamma (IFN-γ), a product of activated CD4+ (Th1) lymphocytes and NK cells, has a key role in the

activation and recruitment of cells, protagonists of cell-mediated immunity. Activated macrophages with a pro-inflammatory phenotype, phagocyte oxidized LDL-cholesterol form the foam cells. Activated macrophages contribute to tissue damage, necrotic lipid core formation, chronic inflammation, and plaque instability by producing different soluble mediators, such as metalloproteinases.

The right side–immune mechanisms responsible for the development of multiple-organ disease, as found in cardio-metabolic conditions, including hypertension, metabolic syndrome and diabetes type 2, and in systemic autoimmune disease. Immune cells transmigrate through the dysfunctional endothelial cells of the microcirculation. The specific immune reaction is initiated by the interaction of activated dendritic cells with naïve, helper (CD4+) type T lymphocytes. The immune reaction develops either towards a humoral (Th2) or cell-mediated (Th1) immune response. Tissue damage or hypoxia create an environment for unresolved chronic inflammation, tissue remodeling and fibrosis. It arises from the imbalance between regulatory immune functions, presented with Treg (regulatory T lymphocytes) and anti-inflammatory cytokines, IL-10 and transforming growth factor beta (TGF-β), and effector immune functions, presented with Th17 lymphocytes, and pro-inflammatory cytokines, IL-23, IL-6, and IL-17A. The established IL-23/IL-17A immune pathway, via the production of Granulocyte and granulocyte macrophage colony stimulating growth factors (G-CSF and GM-CSF), is responsible for the continuous recruitment of activated neutrophils to tissue (increased granulopoiesis). Neutrophils, working in concert with the activated renin-angiotensin system and angiotensin II (Ang II), are the main protagonists of tissue damage and fibrosis.

2. Neutrophil-to-Lymphocyte Ratio (NLR) as a New Cardiovascular Risk Marker

The NLR is calculated from the complete blood count with differential, and is an inexpensive, easy to obtain, and widely available marker of inflammation, with a predictive value comparable to that of CRP. This marker can be used to improve risk stratification in patients with various CVD and cardio-metabolic conditions [12]. A number of researchers concluded that NLR is a more powerful predictor than the total WBC or any of leukocyte subtypes. A reason for this could be that NLR is a ratio of two opposite but complementary immune pathways. On the one hand, it reflects the effect of the neutrophils, that are responsible for nonspecific immune response in inflammation. On the other hand, it reflects the role of lymphocytes, as the critical players in specific immune response. Furthermore, compared to WBC, NLR is much less influenced by physiological conditions, such as physical training or bodily dehydration [12].

In comparison to the effect of each single component of NLR on survival, the reports are consistent in findings that an increased neutrophil count is associated with lower survival, while the situation is more complex in the case of lymphocytes. Namely, reports indicate associations of both, higher and lower lymphocyte counts (lymphocytopenia), with worse outcomes, which depends on the clinical contexts, or there are no reports on these associations at all [13].

Since CVD is a leading cause of death, there is a great interest in strategies for detecting high risk patient groups, by screening in the population [14]. The main cause of these diseases is atherosclerosis. Carotid intima-media thickness is generally accepted as an atherosclerosis stratification risk marker; it correlates well with coronary atherosclerosis and can predict CV events but requires imaging diagnostic methods [15]. A number of studies have identified NLR as an inflammatory marker with good prognostic value in CVD (Table 1). Elevated values for this marker were shown to be associated with CAD and acute coronary syndrome (ACS) and their outcomes and have been reported to predict outcomes in patients undergoing coronary artery revascularization interventions [14]. The NLR has also been shown to be a reliable predictor of short- and long-term mortality in acute cerebrovascular incidents.

Table 1. Published papers in which neutrophil-to-lymphocyte ratio (NLR) was assessed in the context of atherosclerotic cardiovascular disease (CVD).

Authors	Findings
Corriere et al. [16]	**Demonstrated that NLR is a strong predictor of the presence and number of carotid atherosclerotic plaques**
Li et al. [17]	**Demonstrated an association between NLR and mixed and non-calcified plaques in the coronary arteries of patients with chest pain**
Kaya et al. [18]	**Found significantly higher NLR values in patients with severe coronary atherosclerosis**

Authors	Findings
Kalay et al. [19]	Demonstrated that NLR predicts coronary atherosclerosis progression and suggested it as a marker for monitoring
Erturk et al. [20]	NLR values higher than 3.0 were predict CV mortality in patients with peripheral arterial occlusive disease
Tonyali et al. [21]	NLR values equal to or higher than 2.5 were shown to predict severe atherosclerosis with a sensitivity and specificity of 62% and 69%, respectively
Zazula et al. [22]	Found that patients with chest pain that was not caused by cardiac disease, had NLR values of 3.0 ± 1.6, those with chest pain caused by unstable angina had NLR values of 3.6 ± 2.9, and those with MI had much higher values—4.8 ± 3.7 with non-STEMI, and 6.9 ± 5.7 with STEMI, and concluded that NLR value above 5.7 had 91% specificity for the diagnosis of ACS.

In the number of studies, it has been indicated that NLR has a great potential as an easily available laboratory marker for a large number of cardio-metabolic conditions that carry an increased risk of CV and cerebrovascular events (Table 2). However, many of them suggest that their results should be confirmed by further research, to confirm the value of NLR and to better define its role in everyday clinical decisions.

Table 2. Published papers in which NLR was assessed in the context of other cardio-metabolic conditions.

Authors	Findings
Demir et al. [23]	Increased NLR was also found in patients with hypertension of the sort called “non-dipper hypertension”, which does not show a circadian rhythm and is connected with an increased risk of CV events, as a consequence of microvascular changes
Tonyali et al. [21]	Demonstrated in patients with partial or complete nephrectomy, that NLR can represent renal function and renal reserve, making it a good marker of declining renal function
Buyukkaya et al. [24]	Found that increased values for neutrophils and NLR, with an optimal NLR threshold of 1.84, correlate with the severity of MS, without a significant change in the lymphocyte count
Bahadir et al. [25]	Did not find NLR to be a good predictor of inflammation severity in obese patients with MS and without DM2 but indicated that a more significant role was played by CRP and lymphocyte count
Babio et al. [26]	Higher baseline neutrophil counts and an increase in neutrophil counts during follow-up, were both independently associated with a risk of MS in people of 55 years or above, and free of CVD. Although these associations were also seen with total WBC and some other leucocyte subpopulations, neutrophils showed the strongest and most consistent associations, in particular when predicting dyslipidemia associated with MS
Wan et al. [27]	Higher baseline neutrophil counts and an increase in neutrophil counts during follow-up, were both independently associated with a risk of MS in people of 55 years or above, and free of CVD. Although these associations were also seen with total WBC and some other leucocyte subpopulations, neutrophils showed the strongest and most consistent associations, in particular when predicting dyslipidemia associated with MS
Ardahanli et al. [28]	Detected increased NLR values in pre-diabetic patients, compared to healthy controls, suggesting its suitability as a screening marker
Howard et al. [29]	Multiple demographic and lifestyle factors are associated with NLR, independent of important comorbidities, including heart disease, cancer, diabetes, and hypertension

Use of the NLR has also been proposed to improve the diagnosis of chronic conditions other than CVD, the monitoring of disease activity, and the prediction of outcomes, in areas such as malignant diseases, ADs, mental and neurological disorders, such as major depressive disorder, schizophrenia and Parkinson’s disease, supporting the theory of inflammation activation in these conditions, with NLR potentially serving as a marker of inflammatory activity [30].

Despite the growing evidence indicating NLR as a marker that could make a significant change to everyday clinical practice, its implementation in routine practice is still a challenge. This is due to the need to adjust NLR values to patient demographics and health-related factors. Namely, although high NLR values are associated with poorer clinical outcomes, the full range of factors that influence the magnitude of the NLR value are poorly understood. Using data from the NHANES (National Health and Nutrition Examination Survey) survey, Howard et coll. have recently shown that multiple demographic and lifestyle factors are associated with NLR, and independently of important comorbidities, including heart disease, cancer, DM2, and hypertension [29].

Problems that also need to be solved before NLR can be used routinely, are in determining a reference range in a population of healthy people, depending on age and sex, and in determining the thresholds for predicting poor outcomes or adverse disease courses in particular diseases. The study by Forget et al. evaluated NLR in an adult population (22–66 years old) in Belgium, free of acute or chronic diseases, with the aim to determine the reference values, and suggested a normal reference range of 0.78–3.53. Researchers from the Rotterdam study reported a mean value of NLR and the corresponding 95% reference intervals of 1.76 (0.83–3.92), for the general population old 45 years and more [31]. It was shown in this study that NLR increases with age and is higher in males than females.

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