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EDITORIAL COMMENT

Neutrophil-to-lymphocyte ratio and ambulatory blood pressure: Exploring the link between inflammation and hypertension

Relação neutrófilos/linfócitos e pressão arterial ambulatória. Explorando a relação entre inflamação e hipertensão

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In the last decade a strong and definitive link has been established between inflammation and cardiovascular disease. Inflammation occurs in the vasculature as a response to several types of injury. Various risk factors, including hypertension, diabetes, and smoking, together with oxidized low-density lipoprotein cholesterol, trigger a chronic inflammatory reaction, the result of which is a vulnerable plaque, prone to rupture and thrombosis.[1] Epidemiological and clinical studies have consistently shown links between markers of inflammation and risk of future cardiovascular events.[1] Activation of macrophages, T lymphocytes, and smooth muscle cells leads to the release of additional mediators, including adhesion molecules, cytokines, chemokines, and growth factors, all of which play important roles in atherogenesis.[2] Inflammation plays a role in all stages of atherothrombosis, the underlying cause of approximately 80% of all sudden cardiac deaths.[3]

The study by Çimen et al. published in this issue of the *Journal*[4] examines the relationship between 24-hour ambulatory blood pressure (BP) and a systemic inflammation marker, the neutrophil-to-lymphocyte ratio (NLR). The authors claim to have shown for the first time that an increased NLR is independently associated with the severity of hypertension (HTN) in patients with untreated essential HTN. NLR is considered a marker of inflammatory status[5] and has been shown to predict risk of coronary disease,[6] heart failure[7] and stroke,[8] and has been associated with resistant hypertension.[9] Since HTN is a significant risk factor in inflammatory conditions such as atherosclerosis[5] and inflammatory molecules such as C-reactive protein (CRP), vascular and intercellular adhesion molecules, monocyte chemoattractant protein-1 and plasminogen activator inhibitor-1 are increased in HTN,[10,11] the finding of a proportional increase of NLR with higher severity of HTN fits with the hypothesis of the inflammatory nature of hypertensive disease.[12–14] Because inflammation may have a role in the pathogenesis and progression of hypertension,[10,11] the authors speculate that an increase in this inflammatory marker (which can be easily measured in clinical practice) may help to predict HTN severity and to guide therapy in hypertensive patients.

Other indices derived from blood count parameters have also been identified as inflammatory markers, including red cell distribution width (RDW), mean platelet volume (MPV) and platelet-to-lymphocyte ratio (PLR), and some have been associated with different degrees of hypertension severity.[15–17] Some authors have shown that patients with non-dipper hypertension have higher NLR and PLR than

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those with dipper hypertension, although only PLR (not NLR) was found to be an independent predictor of non-dipper status.[18] The most striking aspect of the present study is that HTN was defined on the basis of 24-hour ambulatory BP measurement, in contrast to other authors who used only the less accurate office BP and failed to find any difference in NLR between normotensives and hypertensives. In this study, log NLR values were found to be weakly but positively correlated with 24-hour systolic blood pressure (SBP), diastolic blood pressure (DBP), SBP load and DBP load, while in multivariate analysis, log NLR had an independent association with 24-hour BP and 24-hour BP load. However, one of the major limitations of this type of cross-sectional study lies in the general difficulty of proving causal relationships between variables merely because they appear to be associated in proportion. It is always possible that the relationship between these variables is not direct but rather an epiphenomenon. While not questioning the merit or the novelty of the present study, it would have been of considerable interest to determine whether other inflammatory markers which can be easily measured in clinical practice, such as CRP, RDW, MPV, PLR and leukocyte activation markers, were also seen to be associated with ambulatory HTN, which could thereby have confirmed the coherence, correspondence and validity of the observed data in this population. Also in this context it would have been useful to calculate a receiver operating characteristic curve of the diagnostic value of NLR for HTN.

There is however another finding in this study that deserves some comment. In the interquartile analysis of the NLR distribution, the authors found a relationship between NLR, firstly predominantly with daytime and 24-hour BP values and daytime BP load but not with nighttime BP values, and secondly predominantly with DBP but much less with DBP. This is quite atypical. In several studies[19–24] nighttime SBP and SBP vs. DBP have been clearly shown to be the strongest independent predictors of cardiovascular events and prognosis among the different indices of BP measurement. We may ask why the relationships established in the present study with NLR were not mainly seen with the BP indices that are better determinants of cardiovascular risk (nighttime and systolic BP) but rather with daytime BP and with others with inferior reproducibility and lower predictive value (BP load and diastolic BP). One possible speculative explanation for this atypical finding may be the existence of a circadian rhythm of inflammatory immune responses, with day-to-day and day-to-night fluctuations in immune responses to stress. A number of studies have suggested that sleep disorders such as sleep loss, narcolepsy, and sleep apnea are associated with elevated inflammatory markers such as interleukin 6, tumor necrosis factor-alpha, CRP, and white blood cells.[25–27] For example it has been shown[28] that at the molecular level, >8% of the macrophage transcriptome oscillates in a circadian fashion, including many important regulators for pathogen recognition and cytokine secretion. In addition, time-of-day-dependent fluctuations in the number of neutrophils are not always in line with those of lymphocytes[29] and changes in NLR may be different during day and night. We do not know whether a different NLR measured in blood samples collected at night rather than in the morning could indicate a closer relationship between NLR and nighttime BP values.

A systematic search for inflammatory markers that could enable early detection of the presence of hypertension and its complications in a simple routine blood count is a fascinating challenge. The study by Çimen et al. is within this context. However, further research is needed to precisely determine the scientific robustness of the diagnostic and prognostic value of the association between NLR and HTN at the various stages of the evolution of the disease.

Conflicts of interest

The author has no conflicts of interest to declare.

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