Neutrophil counts and initial presentation of 12 cardiovascular diseases

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For many years, cardiovascular diseases (CVDs) have been the number one cause of mortality in the United States. According to the Centers of Disease Control and Prevention (CDC), heart diseases have led to 614,348 deaths in 2014, which is equivalent to 192.7 deaths per 100,000 population (1). In this perspective, while healthcare providers direct their efforts at controlling the traditional cardiovascular risk factors, researchers are investigating biomarkers which could risk stratify patients and determine prognosis of CVDs.

Several markers were correlated to CVDs in the past two decades, such as red blood cell distribution width (RDW) which has been described as a diagnostic and prognostic factor in CVDs (2). Inflammation is a well-known histopathological finding in atherosclerosis; it also plays a major role in acute coronary syndrome and other CVDs. In this context, multiple studies have suggested the inflammatory marker C-reactive protein (CRP) as an indicator of CVDs (3,4). Other markers including Interleukins have been also linked to atherosclerosis and congestive heart failure (5,6). White blood cells (WBCs) are a major component of all inflammatory processes. Both WBC count and neutrophil to lymphocyte ratio (NLR) have been described as a risk factor, diagnostic factor, or prognostic factor for various CVDs (7-9).

In a recent edition of the *Journal of the American College of Cardiology*, Shah *et al.* showed a correlation between neutrophil count (NC) and 12 CVDs in an adult population (10). They investigated 775,000 adults from the CALIBER (Clinical Research Using Linked Bespoke Studies and Electronic Health Records) registry. This cohort, in the beginning of the study, was shown to have no CVD and was then followed for a median period of 3.8 years during which 55,000 patients developed at least one of the 12 CVDs being studied. The patients were separated into two categories, "acute" and "stable", in order to decrease the selection bias. The first category included patients who were in the hospital at the time of the blood work, or had a recent vaccination, recent infection, recent steroid or methotrexate use, or few other conditions. The second category included all patients who did not fulfill any criteria of the first group. For statistical analysis, Cox proportional hazards models were used for each of the CVDs. Hazard ratios were adjusted for characteristics and comorbidities (10).

This study demonstrated a strong correlation between NC and heart failure (HR: 2.04; 95% CI: 1.82 to 2.29), peripheral arterial disease, unheralded coronary death, abdominal aortic aneurysm and nonfatal myocardial infarction. There was no association between NC and stable angina (HR: 0.97; 95% CI: 0.88 to 1.07), unstable angina, or intracranial hemorrhage. The link with ischemic stroke (HR: 1.36; 95% CI: 1.17 to 1.57) and transient ischemic attack was weak. Interestingly, compared to patients with a lower NC (2×10^9 to 3×10^9/L), those with higher NC (3×10^9 to 4×10^9/L) appeared to have more comorbidities (ex: connective tissue diseases) and cardiovascular risk factors such as diabetes and tobacco use. Detailed analysis of results revealed that NC was associated with TIA in women more often than in men (HR: 1.10 *vs.* 1.07; P=0.001), and associated with an initial presentation of heart failure in men more often than in women (HR: 1.05 *vs.* 1.00; P=0.007) (10).

One of the strengths of the study is the huge sample

size which increases the statistical power. The CALIBER registry (which accounts for 4% of the population of England) appeared to be representative in terms of age, ethnicity, sex, and mortality. Based on previous experience with NLR and RDW, the biggest challenge has always been the establishment of a threshold to be able to confidently associate these values with a cardiovascular risk. Nonetheless, Shah *et al.* were able to overcome this by stratifying NC into intervals, even within the normal range (10).

The study appears to also have some limitations. Like all observational studies, correlation does not imply causation. Conspicuously missing from the analysis was the determination of the linkage between NC and valvular heart disease, and thromboembolism which have been shown to have an association with NLR. However, all the major CVDs were well represented in the study. Also, patients with higher NC were more likely to have more comorbidities, as the elevated NC could be a consequence of those illnesses as opposed to being an independent cardiovascular risk factor. To emphasize this idea, smoking, which was one of these comorbidities, was linked in previous studies to higher NCs; in 1994, Schwartz *et al.* were able to prove that pack-years smoking are an independent predictor of the absolute NC (11).

The CALIBER study is a very important addition to the literature in the quest for identifying biomarkers for the prediction of CVDs. The results suggest that NC may be useful as a predictor of CVD and potentially used in diagnostic and prognostic stratification models.

In recent years, biomarkers have attracted a growing interest. Despite CALIBER not establishing causality, just like most of the previous trials, it is a boost to the search for an available, reliable, and reproducible biomarker as we seek for alternative tools to assist clinicians in diagnosing, monitoring patient response to treatment, and predicting prognosis. Physicians should be aware of this association and an elevated NC should trigger a higher suspicion of CVD.

In this era of modern research, most researchers are focused on developing new and expensive technologies to diagnose, manage and prognosticate diseases. While not mitigating the importance of such research for the advancement of patient care, the studies reviewed here highlight the possibility of finding more utilities in inexpensive material that is already available to us.

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Footnote

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