Neutrophil-to-lymphocyte ratio in acute coronary syndromes: do we (really) need another hero?

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Related article
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According to the 2024 statistics from the American Heart Association, a US citizen suffers an acute myocardial infarction every 40 seconds, which translates into a remarkable 605 000 new ischemic events and 200 000 cases of recurrent attacks per year in the US [1]. More importantly, although the overall incidence of cardiovascular disease showed a downward trend until 2010, the curve reversed thereafter, displaying a gradual increase, magnified during the coronavirus disease 2019 (COVID-19) pandemic, as this life-threatening infectious disease is associated with thrombosis and/or ischemic or non-ischemic myocardial injury [1]. In addition to significant in-hospital mortality and cardiogenic shock, which are approximately twice as high in patients with ST-elevation myocardial infarction (STEMI) compared to those with non-STEMI (NSTEMI) (i.e., 6.4% vs. 3.4%, and 4.4% vs. 1.6%, respectively), there are some other important consequences of cardiac ischemia, the most common of which are recurrence, heart failure and/or dysfunction [1].

The most recent version (published in 2023) of the European Society of Cardiology Guidelines for the management of acute coronary syndromes (ACS) [2] recommends that all patients with suspected myocardial ischemia have serial measurements of high-sensitivity cardiac troponin (hs-cTn). The use of so-called fast-track algorithms (i.e., 0–1/2 hours) has enabled the exclusion of any additional biomarker for early patient assessment, as they are unlikely to add relevant clinical value. In the following period, serum creatinine and natriuretic peptides should also be measured, as they provide additional prognostic information on the risk of death, acute heart failure, and atrial fibrillation as compared to the use hs-cTn alone. The use of other tests such as myosin-binding protein C, C-terminal part of the vasopressin pro-hormone and copeptin is largely debated but arguably cost-effective in facilities using well-validated hs-cTn-based fast protocols. Therefore, the real question at this point in time is "do we (really) need another hero (i.e., biomarker)" in myocardial ischemia? [3].

The answer to this question is based on a fundamental principle: a delicate balance between clinical efficacy (i.e., the ability to diagnose and differentiate different types of myocardial ischemia and/or predict unfavorable outcomes), costs, and widespread availability. Pruc et al. [4] conducted a systematic literature review and meta-analysis to assess whether the neutrophil-to-lymphocyte ratio (NLR) could aid in the diagnosis and/or prognosis of ACS. The authors included 90 articles with 45 990 participants, showing that the value of the NLR ratio was around 1.5-fold higher in patients with STEMI compared to those with NSTEMI, and up to 1.5-fold higher in patients with acute myocardial infarction than in those with unstable angina. The NLR ratio was also useful in distinguishing patients who died from those who survived, as well as those who experienced a major cardiovascular event from those who did not. These findings are encouraging, given that the NLR ratio is a low-cost test (an easy calculation that can be performed manually or even automatically set within the laboratory

information system), that is available in almost all clinical facilities with a basic hematological analyzer. The evidence for its clinical effectiveness overlaps with that for the red blood cell distribution width, another hematological index that has similar diagnostic and prognostic performance in patients with ACS [5]. The NLR ratio, like the red blood cell distribution width, has proven useful in a wide range of human pathologies [6], including COVID-19 [7].

On this premise, a further step must be taken to provide some reliable answers to 3 basic questions: "why does the NLR ratio increase in patients with cardiovascular disease?" and "is this parameter sufficiently standardized?" and, finally, "how should we use this information in the managed care of our patients?".

The first question is only partially answered by Pruc et al. [4], who rely on the fact that the NLR ratio may reflect a process of systematic inflammatory response that often accompanies myocardial ischemia and irreversible cardiac injury. This perhaps convincing explanation points to the major weakness of this parameter, as its value may be significantly elevated in patients with many other conditions, irrespective of the presence of cardiac injury. The specificity of the NLR ratio is hence inherently low, and it cannot be excluded that elevated values may have been triggered by other concomitant pathologies, thus posing challenges to the clinical decision making in the individual patient.

Regarding the second question, although we certainly endorse that this parameter is fast and inexpensive, blood cells can be measured in different ways with the modern generation of hematology analyzers, and their values are not always readily comparable. For example, it has been shown that the neutrophil count is satisfactory correlated when assayed with different hemocytometers, but the lymphocyte count only modestly correlates due to the use of different measurement techniques and dyes [8, 9]. This evidence precludes the establishment of universally validated cut-off values for the NLR ratio, and requires instead a complex process of local validation of diagnostic threshold(s).

The answer to the last question is also challenging. Although we would certainly agree that the NLR ratio could be a good parameter for distinguishing different forms of myocardial ischemia and for predicting their adverse outcome, the best clinical strategy to be used in patients with elevated NLR ratio remains enigmatic. Based on the evidence available to date, it is not possible to determine which biological impairment should be most aggressively addressed. As the NLR ratio appears to reflect an underlying phlogistic condition, it could be argued that the use of anti-inflammatory drugs may be more appropriate in patients with elevated values. To this end, aspirin appears an ideal candidate, combining anti-thrombotic and anti-inflammatory properties. Nevertheless, further studies are certainly needed to determine the best therapeutic options in patients with elevated levels of the NLR ratio.

In summary, the article by Pruc et al. [4] provides good evidence that the NLR ratio is a cost-effective parameter for diagnosis and prognosis of myocardial ischemia, but several other aspects still need to be clarified before it becomes suitable for routine clinical use.

Article information

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