EDITORIAL

Neutrophil-to-lymphocyte ratio: a new prognostic factor even in patients with heart failure

Francesco Dentali, Giulia Conte, Luigina Guasti

Department of Clinical Medicine, Insubria University, Varese, Italy

Heart failure (HF) is a multifactorial disease determined by inability of the heart to deliver oxygen to tissues to meet body's metabolic requirements.[1] HF is extremely common and progressively increases with age; its incidence reaches from 5 to 10 persons per 1000 per year for an estimated prevalence of 1% to 2% of the adult population in the Western world.[2] Unfortunately, despite the progress in the treatment of this disease, its prognosis is still poor with a 40% risk of death or readmission to the hospital at 1 year.[1,3] Thus, adequate risk stratification appears to be of paramount importance for the management of HF patients. Typically, several clinical characteristics such as age, sex, New York Heart Association classification, cause of HF, and the presence of relevant comorbidities have been evaluated to assess the prognosis of patients with HF. Furthermore, an echocardiographic assessment of ventricular function indices (ejection fraction, ventricular mass) is considered essential for their risk stratification.

The evaluation of a number of laboratory biomarkers has been proposed to complement the prognostic assessment of HF patients. B-type natriuretic peptide and its inactive form, N-terminal pro-B-type natriuretic peptide, are widely used in diagnostic workup of patients with suspicion of acutely decompensated HF. Beyond their value for diagnostic evaluation, natriuretic peptides have been shown in numerous studies to be useful also in stratifying the risk for rehospitalization and death of these patients.[4] Highly sensitive troponin provides important prognostic information in the context of acute decompensated HF and seems to play an integral role in the evaluation of HF patients. Concentrations of soluble ST2, a protein found to be upregulated in the case of mechanical strain in cardiac myocytes, have been associated both with HF symptom severity and with risk of short- and long-term mortality.[5] Furthermore, soluble ST2 monitoring has demonstrated to be potentially useful also in therapeutic decision making in these patients.[5] Thus, all these biomarkers have emerged as being potentially useful for the practicing clinician.

A number of studies have shown that neutrophils are independent predictors of a poor clinical outcome in various cardiac diseases, including stable coronary artery disease as well as acute coronary syndromes.[6] Moreover, neutrophil-to-lymphocyte ratio (NLR) has been found to be a negative predictor of all-cause mortality in patients undergoing coronary angiography or invasive revascularization.[7] Neutrophils probably act directly to determine myocardial tissue damage besides being part of the acute inflammatory response to tissue injury.[7] In patients with acute coronary syndromes, neutrophils are functionally activated and local neutrophil infiltration has been documented in culprit plaque lesions suggesting the role of neutrophils in destabilization of atherosclerotic plaques.[8] Furthermore, activated polymorphonuclear leukocyte-derived microparticles may enhance coagulation and promote thrombus formation thanks to platelet activation and their expression of P-selectin. Thus, the NLR may be considered a new systemic inflammatory marker and has been proposed as a risk stratification index in order to predict long-term mortality in patients with several cardiovascular diseases.

A number of studies have suggested an involvement of the immune system also in the pathogenesis and progression of HF.[8] A low-grade inflammatory response, as a result of various stimuli (ischemia, infection, toxins, neurohormonal activation), appears to be necessary to start the repair of the injured heart, but it may also contribute to death of cardiac myocytes, hypertrophy, fibrosis, and loss of the normal cardiac structure. In the acute phase, progression to HF can be due to a consistent loss of myocytes, and in the

Correspondence to:
Francesco Dentali, MD, L'Unità Operativa di Medicina Interna, Ospedale di Circolo, Viale Borri 57, 21100 Varese, Italy, phone: +39 0332 278 594, e-mail: fdentali@libero.it
Received: March 6, 2016.
Accepted: March 6, 2016.
Published online: March 23, 2016.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2016; 126 (3): 116-117
doi: 10.20452/pamw.3331

chronic phase, it may be due to a low-level apoptosis. Cell death is localized both in the affected ischemic zone and also in the more remote myocardium, which consequently leads to a reduction in contractile reserve and to progression of HF.

A few studies have assessed the prognostic role of the NLR in patients with HF.[9,10] In the current issue of *Polish Archives of Internal Medicine* (Pol Arch Med Wewn), Wasilewski et al,[11] using data of the COMMIT-HF registry, reported important findings on the role of the NLR in predicting long-term mortality in patients with HF of different etiologies. In this large cohort (1734 patients), a high NLR was significantly associated with an increased risk of 12-month all-cause mortality in the subpopulation of patients with an ischemic etiology of HF, but not in patients with a nonischemic HF. As underlined by the authors, the NLR is an inexpensive and may generally be measured in all HF patients admitted to the hospital. In addition, considering the frequency of ischemic origin of HF and the prognosis of these patients, the evaluation of the NLR may be particularly useful for clinicians.

If the results of Wasilewski et al[11] are confirmed in other large prospective studies, the NLR may be evaluated along with other prognostic markers in all patients presenting with HF of ischemic origin to improve the risk stratification of these patients. Furthermore, the results open the way to other studies that may evaluate new therapeutic approaches in these patients. Statins and tumor necrosis factor-α inhibitors have been proposed to modify the inflammatory status of patients with several cardiovascular and noncardiovascular diseases.[12] Assessment of the NLR in patients with HF may help identify the subgroup of patients who may derive more benefit from treatment with these drugs. However, we have to wait for the results of high-quality randomized controlled trials in this setting before implementing these findings to clinical practice.

REFERENCES

1 Braunwald E. Heart failure. JACC Heart Fail. 2013; 1: 1-20.

2 Mostered A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007; 93: 1137-1146.

3 Cowie MR, Wood DA, Coats AJ, et al. Survival of patients with a new diagnosis of heart failure: a population based study. Heart. 2000; 83: 505-510.

4 Januzzi JL, Van Kimmenmade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J. 2006: 27: 330-337.

5 Breidthard T, Balmelli C, Twerenbold R, et al. Heart failure therapy-induced early ST2 changes may offer long-term therapy guidance. J Card Fail. 2013: 19: 821-828.

6 Guasti L, Dentali F, Castiglioni L, et al. Neutrophils and clinical outcomes in patients with acute coronary syndromes and/or cardiac revascularisation. A systematic review on more than 34,000 subjects. Thromb Haemost. 2011; 106: 591-599.

7 Naruko T, Ueda M, Haze K, et al. Neutrophil infiltration of culprit lesions in acute coronary syndromes. Circulation. 2002; 106: 2894-2900.

8 Briasoulis A, Androulakis E, Christophides T, Tousoulis D. The role of inflammation and cell death in the pathogenesis, progression and treatment of heart failure. Heart Fail Rev. 2016; 21: 169-176.

9 Uthamalingam S, Patvardhan EA, Subramanian S, et al. Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensate heart failure. Am J Cardiol. 2011; 107: 433-438.

10 Benites-Zapata VA, Hernandez AV, Nagarajan V, et al. Usefulness of neutrophil-to- lymphocyte ratio in risk stratification of patients with advanced heart failure. Am J Cardiol. 2015; 115: 57-61.

11 Wasilewski J, Pyka L, Hawranek M, et al. The prognostic value of neutrophil-to-lymphocyte ratio in predicting long-term mortality in patients with ischemic and non-ischemic heart failure. Pol Arch Med Wewn. 2016; 126: 167-173.

12 Moreira DM, da Silva RL, Vieira JL, et al. Role of vascular inflammation in coronary artery disease: potential of anti-inflammatory drugs in the prevention of atherothrombosis. Inflammation and anti-inflammatory drugs in coronary artery disease. Am J Cardiovasc Drugs. 2015; 15: 1-11.