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Original Article

Neutrophil to lymphocyte ratio as a predictor of myocardial damage and cardiac dysfunction in acute coronary syndrome patients

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ABSTRACT

Background: Neutrophil to lymphocyte ratio (NLR) in peripheral blood is established to correlate with the morbidity and mortality of heart disease patients. We aimed to define the severity of inflammation (NLR) by observing the association of NLR with cardiac functions or myocardial damage parameters in patients with acute myocardial infarction.

Methods: Data from 715 patients who underwent percutaneous coronary intervention (PCI) within 72 hours of incidence in 2016 were analysed retrospectively.

Results: The NLR ranges from 0.50 to 46 (medium ± SD, 2.76 ± 2.96) in 715 patients. NLR positively correlated with myocardial damage (NLR vs. CK-mB: $p < 0.0001$) but negatively correlated with myocardial function (NLR vs. EF: $p < 0.0001$; NLR vs. FS: $p < 0.0001$). Myocardial damage markers (CK, CK-mB, ASL, LDH) were significantly increased, and cardiac contractile parameters (EF and FS) were reduced at NLR > 2.76 compared to those of NLR < 2.76. ELISA analysis has shown that IL-10 was significantly increased when NLR ≥ 4.6 and TGF-β were increased at NLR > 4. The correlation was diminished between NLR and CK-mB at NLR > 2.76 or at NLR > 4, but that of NLR and EF or FS was maintained in NLR > 2.76 and at NLR > 4. EF and FS were comparable between NLR > 2.76 and NLR > 4. But myocardial damage parameters increased significantly at NLR > 4 compared to those of NLR > 2.76.

Conclusion: NLR is a strong predictor of myocardial damage in acute myocardial patients. High NLR are associated with myocardial dysfunction in all the patients. Severe inflammation (NLR) can predict the consequence of the heart in patients with coronary syndrome.

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1. Introduction

Cardiovascular diseases are the number one causes of mortality in humans worldwide, and coronary syndrome (myocardial infarction, MI) is one of the prevalent conditions; those are responsible for fatal heart attack and heart failure.[1] Impaired vascular perfusion in MI and reperfusion cause the damage of the myocardium, depending on the duration of ischaemia and metabolic demand of the tissue. As a consequence, systematic and local inflammation can be triggered, which is important in the remodelling and the scar formation of the myocardium.[2–4]

There are two main phases of inflammation during MI: the inflammatory phase and the proliferative phase. Neutrophils are the first leukocytes to be found in damaged area. Their activation produces large amounts of inflammatory mediators, and those regulate the response to tissue injury demonstrating hypoxic damage through ROS, proteolytic enzymes and other mediators.[4–6] At the infarct site, neutrophils release free radicals which act as an injury pathway for cardiomyocytes. The release of proteo-enzymes helps the clearance of the infarct and also amplifies immune cell recruitment (in particular M1 macrophage). As such, neutrophils are involved in not only inducing macrophage to the infarct site, but also allowing the clearance of debris.[7–10]

In contrast, lymphocytes play vital roles in the remodelling of the myocardium following inflammation. For example, CD4+ T regulatory cells constitute a particular anti-inflammatory immune regulatory lymphocyte subset which is generated in the thymus and highly enriched for T cells with autoantigen specificity.[11] T cells are essential for the recruitment of proangiogenic macrophages and collateral artery formation.[11–13] B cells are involved in monocyte recruitment through the CCL7 pathway.[2,11–14] The clearance of debris, activation of fibroblasts and collagen deposition for scar formation and neovascularisation (the proliferative phase) occur 3–4 days after MI.[8,14,15] The release of inflammatory and anti-inflammatory mediators (IL-10, TGF-β and pro-resolving mediators, [8,14,16]) from neutrophil or lymphocyte cells promotes neutrophil apoptosis and phagocytic uptake by macrophages.[9,10,15] IL-10 secreted by T lymphocytes inhibits the production of inflammatory cytokines, stabilises the matrix and regulates ECM metabolism. Macrophages engulfing apoptotic neutrophils are a key activator of the anti-inflammatory response and potent inhibitor of pro-inflammatory cytokines.

Neutrophils are seen as a marker of ongoing inflammation and lymphocytes as a marker of regulatory pathways. Neutrophil-to-lymphocyte ratio (NLR) (calculated via dividing neutrophil count by lymphocyte count) as an indication of systemic inflammation has been demonstrated to be associated with poor clinical outcomes in various cardiovascular diseases, including acute coronary syndrome. Recent accumulating evidence points that high NLR to be independently and strongly associated with increased risk of complications and mortality post-acute MI.[5,17–24] Here, our aim is to evaluate the level of NLR that is associated with myocardial dysfunction (EF and FS from echocardiography) or damage (CK-mB) in 715 myocardial infarction patients. NLR is readily available, so it may be used as a cost-effective adverse predictor.[5,21]

2. Methods

2.1. Patients

Data from 1111 patients who underwent PCI 72 hours after the onset at Yanbian University Affiliated Hospital, Jilin province in China (from January 2015 to December 2016) were analysed retrospectively. We excluded 396 patients who had inflammatory diseases such as gastritis, chronic cholecystitis, nephritis, rhinitis, pharyngitis, bronchitis, myocarditis, rheumatoid arthritis, gout, immune system disorders and cancer in analysis group, and the count of cohort in the study was 715. Basic demographics, history, diagnosis at presentation, blood pressure, weight, complete blood count and echocardiogram results were obtained. The study was approved by the Ethical Committee of Yanbian University Hospital with the informed consent to the patients.

2.2. Statistical analysis

All analyses were performed using SPSS 23. The main parameters tested were: "NLR ratio" as the independent variables. The dependent variables were "EF", "FS" and "CK-mB". Pearson's correlation was performed, and correlation and p values were obtained to assess the strength of any association between variables. The descriptive statistics function on SPSS 23 was used for details on the overall data and the parameters were expressed as means ± SD. Firstly we analysed all the patients together. Next, we divided each of the groups into high NLR and low NLR. CK-mB in different NLR groups was expressed as means ± SE. The cut-off NLR value was 2.76, which was the median value of 715 patients. Student unpaired t-test (followed by Bonferroni correction) was used for testing the significance of the parameters between groups. Scatter plot graphs were used to demonstrate visually whether there are any relationships. $p < 0.05$ was considered significant.

2.3. Detection of inflammatory and anti-inflammatory cytokines from arterial blood samples

Blood samples were drawn from the coronary artery before PCI procedure. The IL-10 and TGF-β concentration in the plasma was measured by using an enzyme-linked immunosorbent assay (ELISA).

3. Results

A total of 715 patients with myocardial infarction who underwent PCI with stent within 72 hours of symptom onset were enrolled in our study. The mean age was 61.38 (±9.84) years, and 417 (58.32%) of the patients were men. The baseline clinical characteristics of myocardial function (e.g., EF, FS and SV) and myocardial damage (e.g., LDH, CK, CK-mB, AST) were shown in Table 1. The mean NLR of cohort was 2.76 ± 2.96.

In all the patient groups, there was a positive linear regression of NLR versus CK-mB ($r = 0.264$, $p < 0.0001$), negative linear regression of NLR versus EF ($r = -0.208$, $p < 0.0001$) or FS

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