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Review Article

Neutrophil-Lymphocyte Ratio Value as a Predictor of Troponin Elevation in Patients with Non-ST Segment Elevation Acute Coronary Syndrome

Lutfi Hafiz Zunardi[1*], Setyasih Anjarwani[2], Indra Prasetya[2], Anna Fuji Rahimah[2]

[1]Brawijaya Cardiovascular Research Center, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
[2]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.

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ABSTRACT

Acute coronary syndrome (ACS) is a prominent contributor to mortality and morbidity on a global scale, consistently ranking within the top five primary causes. Inflammation is one of the many elements that have a role in the pathophysiology of the development and destabilization of plaque atherosclerosis in ACS. Troponin is a component of a biomarker that signals damage to the heart muscle in ACS patients; however, at the present time, not all medical facilities are able to perform troponin testing. An acute myocardial infarction begins with an initial inflammatory process that generates proinflammatory cytokines at the cellular level. This can be evaluated by the NLR through peripheral blood tests. The NLR as an indication of systemic inflammation has been demonstrated to be associated with poor clinical outcomes, an increased risk of complications, and mortality in ACS patients. In addition, several studies showed that the NLR has prognostic value in patients with ACS. The NLR is a mix of inflammatory markers, which can be a predictor of increased troponin in cases of non-ST segment elevation acute coronary syndrome (NSTEACS) in an emergency room.

1. Introduction

ACS is widely recognised as a prevalent etiological factor contributing to life-threatening heart attacks and heart failure, hence establishing cardiovascular disease as the foremost cause of mortality worldwide.[1] When discussing myocardial infarction, or heart attack (MI), the myocardium receives damage due to inadequate arterial perfusion and subsequent reperfusion. The extent of this damage is influenced by the length of the ischemia and the tissue's metabolic requirements. Therefore, systemic and local inflammation can be generated, which is pivotal in heart remodelling and scar formation in ACS.[2,3] ST elevation myocardial infarction (STEMI) can be diagnosed with chest pain and an ECG. However, NSTEACS is harder to diagnose because, in addition to an abnormal ECG, a cardiac enzyme examination is needed to show myocardial damage and tell the difference between unstable angina pectoris (UAP) and non-ST segment elevation myocardial infarction (NSTEMI).[4–6]

The neutrophil-to-lymphocyte ratio (NLR) serves as an indicator that establishes a connection between two components of the immunological system as follows: the innate response to infection, spearheaded by neutrophils, and adaptive immunity, assisted by lymphocytes. It is found by taking the ratio of the numbers of neutrophils and lymphocytes in the peripheral blood. Neutrophils are the first protective mechanism against viruses that enter the body. They do this in a number of ways, such as by chemotaxis, phagocytosis, releasing reactive oxygen species (ROS), granular proteins, and making and releasing cytokines.[7,8] The NLR is a marker of systemic inflammation that has been linked to worse clinical outcomes across a spectrum of cardiovascular disorders. In addition to the increased risk of morbidity and mortality after acute MI, high NLR has been shown in recent studies to be substantially associated with its possible predictors of troponin elevation.[9] Due to its accessibility, NLR has the potential to serve as a low-cost replacement for cardiac enzymes.

2. Acute Coronary Syndrome

The main feature of ACS is an abrupt decrease in blood supply to the heart muscle, leading to the development of unstable angina, myocardial infarction with no ST elevation (NSTEMI), and ST-elevation myocardial infarction (STEMI). If at least one test result is higher than the top 99th percentile level, high-sensitivity cardiac troponin (hs-cTn) T or I is the best way to find out if someone has had an acute myocardial infarction (AMI). However, other cardiac indicators could also be applied in a comparable way.[6]

As a result, several researchers have focused on ACS's pathophysiology and hypothesized three primary pathophysiological processes. The first is the bursting of lipid-rich, fibrous-capped atherosclerotic plaques. Platelet activation and thrombosis come from metalloproteinases (MMP) degrading the fibrous cap, causing rupture and necrosis of the revealed core in the arterial lumen[10]. Second, plaque erosion happens when the fibrous cap covering the atherosclerotic

* Corresponding author at: Brawijaya Cardiovascular Research Center, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
E-mail address: lutfi.hafiz.lh@gmail.com (L.H. Zunardi).

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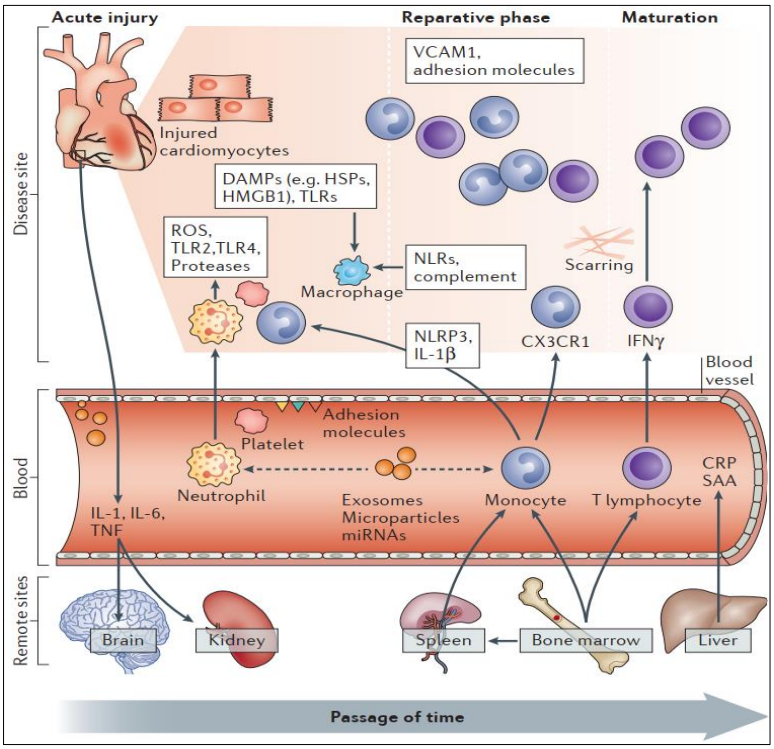

Figure 1. Acute coronary syndromes are caused by a variety of different factors.[12]

plaque is not destroyed but thrombus development occurs around the plaque's edge due to endothelial desquamation. In the absence of thrombosis, the third mechanism involves coronary vasospasm and myocardial bridging (MB), both of which are not attributable to atherosclerosis.[11] Several mechanisms for the occurrence of an ACS are described in Figure 1.[12]

The development of atherosclerosis is controlled by both proinflammatory and anti-inflammatory innate and adaptive immune cells. ACS is exacerbated by the progression of stable plaques to instability plaques, which leads to plaque rupture or erosion and thrombus development. As a result, inflammatory responses, both systemic and local, are major contributors to ACS. Plaque rupture can be brought on by mental strain or by pressure on the walls of the artery in a specific area. Similar to how macrophage-mediated inflammation has nothing to do with coronary plaque erosion with white thrombus, platelet aggregation is the cause of this complication Coronary plaque erosion is not directly linked to systemic inflammation, even though research has indicated that the immune system and inflammatory mediators are involved.[10,13] The impact of inflammation and the immune system on the development of acute coronary syndrome is explained in Figure 2 and 3.

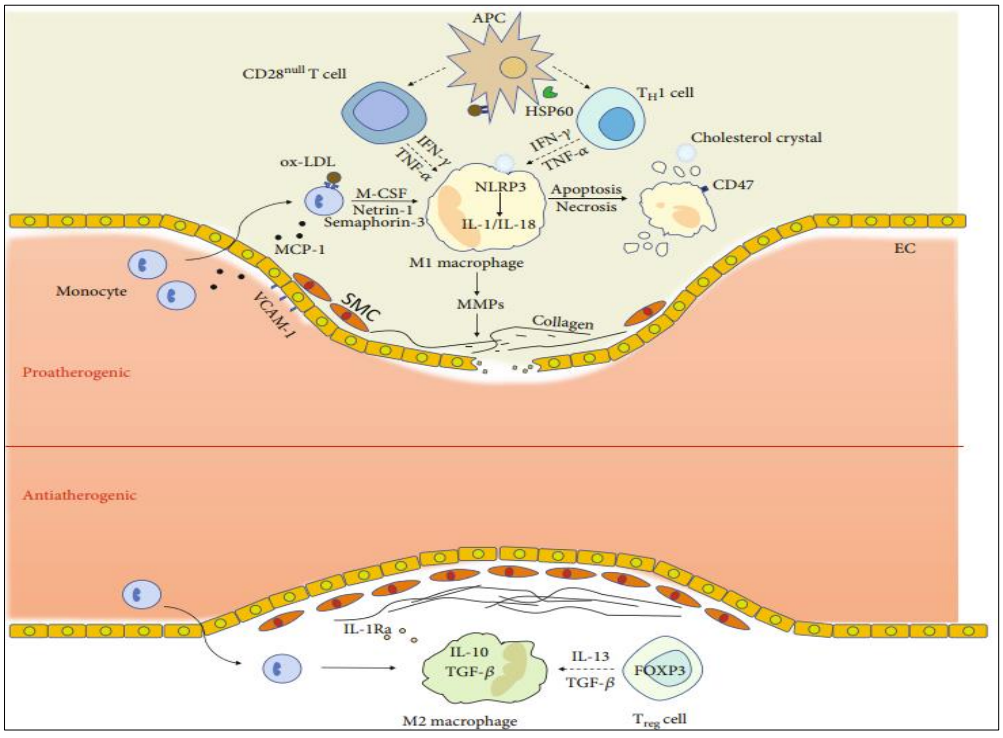

Figure 2. The roles of the immune system and inflammation in the development of acute coronary syndrome.[8]

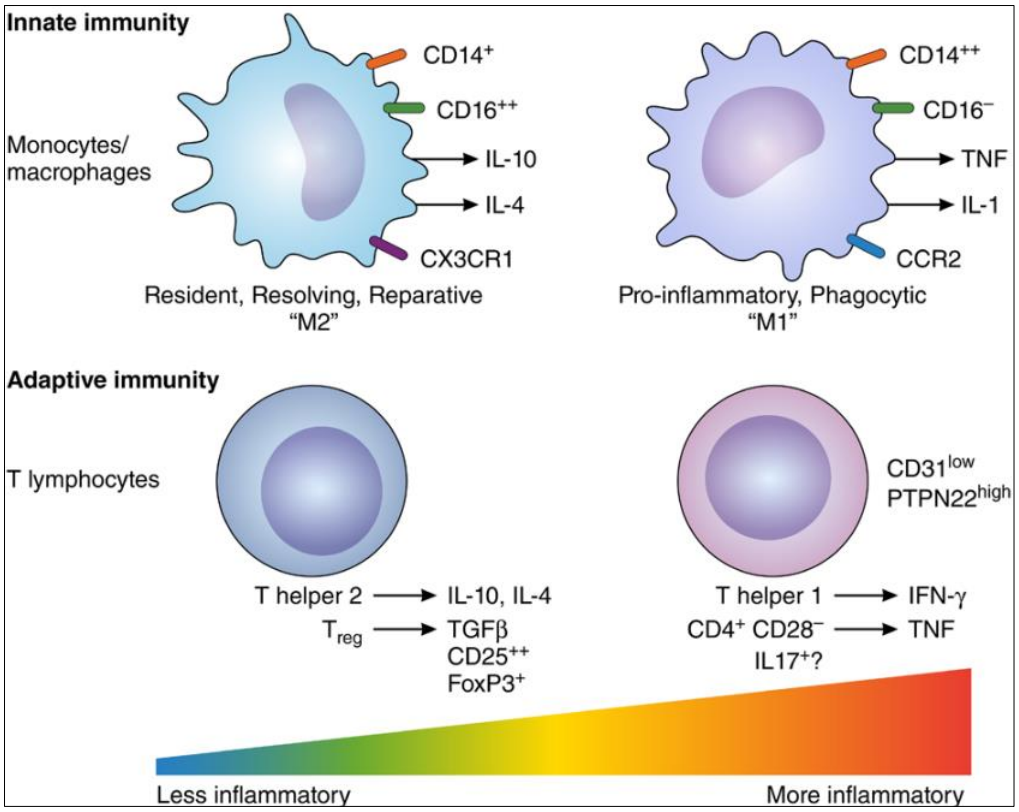

Figure 3. Atherosclerotic plaque activity may be regulated by an imbalance in adaptive immune mechanisms.[10]

3. Neutrophil to Lymphocyte Ratio

To determine the NLR, divide the whole neutrophil count by the overall lymphocyte count. Neutrophils proliferate and lymphocytes shrink in response to physiological stress. The NLR takes advantage of both of these variations to increase its sensitivity. Potentially important factors in the NLR include endogenous cortisol and catecholamines. It is well established that elevated cortisol causes an increase in neutrophils and a decrease in lymphocytes.Other hormones are probably involved as well. Therefore, NLR is not exclusively related to infection or inflammation. Hypovolemic shock, acute coronary syndrome, sepsis, bacteremia, pancreatitis, and appendicitis are all examples of physiological stress that may cause an increase in the NLR. NLR increases precipitously after only 6 hours of physiological stress. NLR may be a more reliable indicator of acute stress than other, slower-responding labs (such as white blood cell count or bandemia). Influencing factors of neutrophil-lymphocyte ratio (NLR) include age, race, medications (corticoids), and chronic diseases like ischemic heart disease, chronic heart disease, anemia, diabetes, obesity, depression disorders, and cancer.[14]

4. Leukocytes in ACS

There are two basic types of white blood cells in clinical practise: granulocytes, which have easily visible cytoplasmic granules, and agranulocytes, which are mononuclear white blood cells and lack these granules. Granulocytes include neutrophils, eosinophils, and basophils; agranulocyte leukocytes include monocytes and lymphocytes. By contributing to the destabilisation of atherosclerotic plaques, Leukocytes are known to have a pivotal role in the pathophysiology of acute coronary syndrome. Leukocytes enter endothelial cells and stimulate them after they penetrate the tunica intima in the first phase. Plaque vulnerability is increased because of the microvascularity they cause to occur.[15] High amounts of the surface protein Ly6c show that inflammatory substances leukocytes, a type of monocyte, are accumulating in the circulatory system. These proinflammatory monocytes draw attention to new atherosclerosis plaques, mostly through macrophage chemoattractant protein (MCP)-1 reacting with its CC chemokine receptor (CCR)-2.[16]

Whereas enhanced mobilisation seems to be responsible for the formation of these cells in developing plaques, their replication is the primary mechanism causing their increasing quantity in preexisting plaques. Macrophage colony-stimulating factor (M-CSF/CSF-1) is a haematological growth factor necessary for the proliferation of mononuclear phagocytes within the atheroma.[16] Several research studies have demonstrated a correlation between leukocytosis and an elevated rate of cardiovascular death.[17] Individuals with ACS had an increased chance of dying in the 30 days and 6 months after their myocardial infarction if their WBC count was high. The raised rate of death among individuals with ACS has been linked to the higher concentration of leukocytes on hospitalisation, which has been linked to greater microvascular damage, congestive heart failure, and shock.[18]

5. Role of Lymphocytes in ACS

After the beginning of myocardial infarction, a substantial number of T and B cells are recruited to the site of heart injury to initiate the specific immune reactions necessary for healing the wound.[19] Helper T cells (Th), regulatory T cells (Tregs), and CD8+ T cells (Tc) are all subsets of CD4+ T cells, which exert immunological functions via circulation in the blood and lymph system.[20-21] Myocardial infarction (MI) triggers the stimulation of T cells by identification of heart-specific antigens, and CD4+ T cells aid in the repair of damaged tissue.[22] Apoptosis, unfavorable ventricular remodeling, and impairment of cardiac performance are all caused by the recruitment and activation of CD8 T lymphocytes in ischemic cardiac tissue post acute MI in mice.[23]

B lymphocytes have the capacity to impact inflammation and remodeling subsequent to MI. When mature B lymphocytes bring inflammatory mediators monocytes to the heart, the area of an infarction gets bigger and the cardiac performance gets worse.[24] Improving cardiac function and reducing infarct size after MI is considerably aided by raising the number of B cells from bone marrow, however this proliferation of bone marrow B cells terminates within 24 hours of MI.[25] Lymphocytes play a complex function in MI, adding complication to an already challenging disease to treat. To learn how lymphocytes can play a part in effective, specific treatment, we need to pinpoint the exact moment when MI occurred.

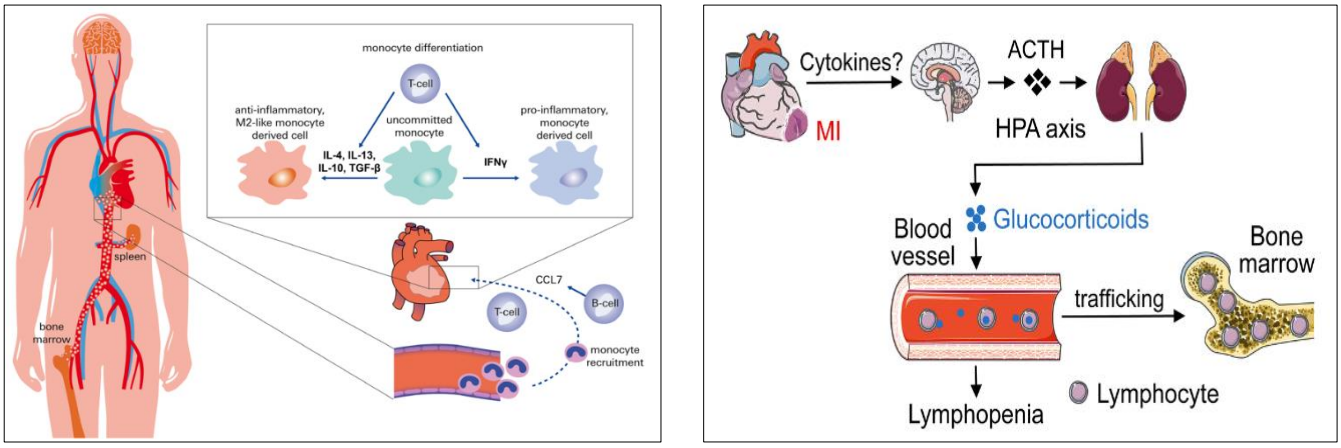

Figure 4. (A) The mechanism of activation, recruitment of lymphocytes, and (B) The mechanism of lymphopenia in acute coronary syndrome.[26,37]

After a MI, the body's leukocyte count drops due to a decrease in lymphocytes and an increase in granulocytes. We found that post-MI bone marrow naive B cells were halted by doing single-cell RNA sequencing (scRNA-Seq) study. Insufficient lymphocyte numbers have been linked to unfavourable outcomes. coronary artery disease and persistent heart failure people with cardiovascular disease. Potential primary NLR drivers include catecholamines and endogenous cortisol. It is widely known that elevated cortisol levels result in an increase in neutrophils and a decrease in lymphocytes. Both low lymphocyte counts and high leukocyte counts can be caused by endogenous catecholamines like adrenaline. It's also possible that hormones like cytokines play a role.[25,26] The mechanism of activation, recruitment of lymphocytes, and lymphopenia in acute coronary syndrome is explained in Figure 4.

6. Neutrophils in ACS

In the days before an acute myocardial infarction (AMI), polymorphonuclear leukocytes (PMNs) from the bone marrow travel through the bloodstream and are the first inflammatory cells to show up in the damaged myocardium. They are most common on days 1 and 3 and start to drop off by day 5. At reperfusion, neutrophils accumulate more heavily in the MI's periphery than they did before. There is an elevated level of chemotactic factors in the damaged myocardium, and these factors draw in PMNs. These factors include macrophage inflammatory protein-2 (MIP-2, CXCL2, GRO), leukotriene B4 (LTB4), cytokine-induced neutrophil chemoattractant 1 (CINC-1, CXCL1, GRO, KC), and interleukin 8 (IL-8, CXCL8).[3]

They travel across the endothelium of post-capillary venules and into the injured myocardium in three different stages. First, the PMNs attach to P-selectin, E-selectin, intercellular adhesion molecules (ICAMs), and vascular cell adhesion molecules (VCAMs) on endothelial cells that have been stimulated. This makes the PMNs stick to the cells and roll on them. The PMN integrins L2 and M then bind with their endothelial cell ligands, ICAM-1 and ICAM-2, to form a strong adhesion in a second stage. Integrins L2 and M2, and intercellular adhesion molecule 1 (ICAM-1) and molecule 2 (ICAM-2) all play a role in PMN trans-endothelial travel across endothelial cells.[3] Clinical practice dictates that patients experiencing total coronary blockage, myocardial ischaemia, and chest discomfort get early reperfusion therapy within anywhere from 3 to 6 hours of symptom onset. Unfortunately, reperfusion can also cause harm to the myocardium and enlarge the infarct. Some research has demonstrated that neutrophil-depleted blood, rather than whole blood, can reduce infarct size after reperfusing. The signals released by dying myocardium and damaged extracellular matrix upon reperfusion actually draw in and stimulate neutrophils.[27] At first, this supports in myocardial healing because neutrophils consume dead tissue and attract in more tissue-degrading monocytes.[28] It is possible that the infarct size is increased by the activation of neutrophils, which causes them to generate degranulated proteins and reactive oxygen species that damage intact cells and extracellular matrix, activate endothelial cells, and recruit even more neutrophils. Furthermore, it has been demonstrated that enhanced migration of monocytes post MI accelerates atherosclerosis in rats, lending credence to the notion that neutrophil-mediated recruitment of monocytes is deleterious over the long run. Clinical evidence of higher occurrences in MI survivors lend credence to this finding.[29]

7. Neutrophil to Lymphocyte Ratio in ACS

The ratio of neutrophils to lymphocytes in a differential white blood cells (WBC) sample can be used to calculate NLR. It is one of the most highly evaluated hematological indicators available for use in the diagnosis and prognosis of ACS. Comprehensive research in recent years has focused on its possible significance in diseases of the cardiovascular system.[30]

The presence of polymorphonuclear cells (PMN), specifically active neutrophils, was seen in coronary thrombi of patients with myocardial infarction. Neutrophil extracellular traps (NETs) are released by polymorphonuclear leukocytes (PMNs) at the location of the culprit lesion. Neutrophil extracellular traps (NETs) are fibrous structures that exhibit a strong proinflammatory and prothrombotic nature, capable of entrapping leukocytes and promoting the formation of blood clots. The study demonstrated a negative correlation between neutrophil extracellular traps (NETs) and ST-segment resolution (STR), as well as a positive correlation between NETs and infarct size.[31] On the other hand, lymphocytes, specifically B2 and T helper cells, serve as integral components of the adaptive immune system and possess the ability to suppress and restrict inflammation. Changes in the immune system that occur quickly in response to ACS can be seen in the decreased number of lymphocytes and the increased number of neutrophils. One of the first symptoms of acute myocardial infarction is a decrease in lymphocyte count, which has been linked to stress-induced cortisol release.[32] The effects of neutrophils on atherosclerosis, thrombosis, and ischaemia-reperfusion injury are explained in Figure 5.

Combining the NLR features improves prediction over using either one separately. The relationship between NLR and the advancement of coronary atherosclerosis, a robust and autonomous prognostic of upcoming coronary events, is established.[33] Patients with STEMI and NSTEMI have seen an increase in the number of research studies examining the NLR's potential as a prognostic biomarker for short- and long-term survival in the past few years.[34] A greater A relativerisk (RR) of mortality from all causes was found in a meta-analysis comprising eleven cohorts. increased risk of cardiovascular events in individuals undergoing angiography or cardiac revascularization (RR = 1.99) and elevated NLR levels in comparison to those with low NLR levels (RR = 2.33). Increased odds of in-hospital death (OR = 2.04) were observed in a study of 2,833 individuals with acute coronary syndromes who were part of an observational cohort.[35]

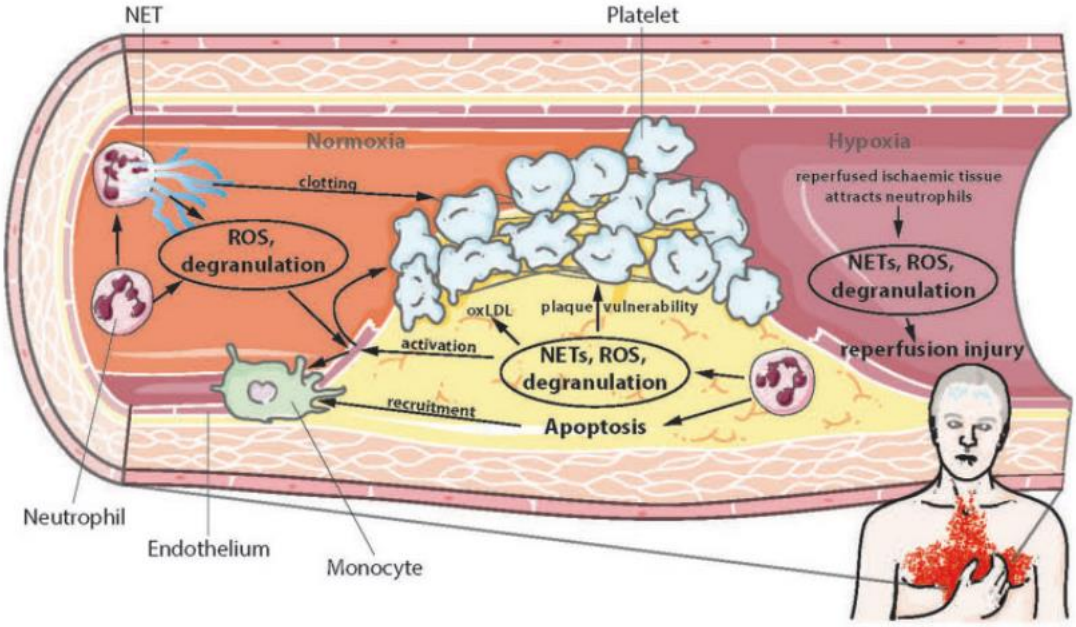

Figure 5. Neutrophil effects in ischemic, thrombotic, and reperfused tissue injury. Oxidized low-density lipoprotein (oxLDL), reactive oxygen species (ROS), and neutrophil extracellular traps (NETs).[38]

The significant survival rate of patients with ST-elevation myocardial infarction (STEMI) is something that can be avoided with the use of NRL. A NLR > 4.9 was associated with a 70% sensitivity to hospital death predictions and a 65% specificity. Multivariate study revealed a robust association between NLR and stent thrombosis. The SYNTAX score, the GRACE scale, and the TIMI score are also used to evaluate the degree of difficulty and severity of ACS, which is then referred to in NRL. A different study confirmed the high predictive value of the NLR for elevated troponin levels.[36]

8. Conclusion

Endothelial dysfunction has a strong connection to the inflammatory process, serving as the primary mechanism underlying the development of ACS. ACS is primarily due to the disintegrate of atherosclerotic plaque accompanied by the formation of a thrombus. Consequently, inflammation assumes a crucial role in the pathophysiology of acute coronary events. The NLR has been identified as a strong indicator of future death from cardiovascular disease. NLR plays a prognostic function in determining mortality for patients with a diagnosis of stable CAD. NLR is a well-validated biomarker of systemic inflammation in patients with ACS. Elevated NLR is associated with a higher risk of death and hospitalisation from a variety of cardiovascular illnesses, including heart attacks and strokes.

Based on comprehensive discussions and current scientific investigations, a strong relationship has been discovered between the elevated NLR and elevated levels of cardiac Troponin I in patients exhibiting symptoms suggestive of NSTEACS. Therefore, the application of NLR, as a cost-effective and efficient approach, has the potential to serve as a predictor for the increase in cardiac Troponin-I levels in patients who exhibit symptoms indicative of NSTEACS.

9. Declaration

9.1 Ethics Approval and Consent to participate
This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involvement in the study.

9.2. Consent for publication
Not applicable.

9.3 Availibility of data and materials
Data used in our study were presented in the main text.

9.4 Competing interests
Not applicable.

9.5 Funding Source
Not applicable.

9.6 Authors contributions
Idea/concept: SA. Design: LHZ. Control/supervision: SA, SW, VY. Data collection/processing: LHZ. Analysis/interpretation: LHZ, SA. Literature review: LHZ. Writing the article: LHZ. Critical review: SA, SW, VY. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

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