International Journal of Multiphysics
Volume 18, No. 3, 2024
ISSN: 1750-9548

Role of Systemic Immune Inflammation Index in Coronary Artery Disease

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Abstract:

Background: Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality worldwide, primarily driven by atherosclerosis, which is now recognized as a chronic inflammatory process. Inflammation and immune activation contribute to every stage of atherogenesis, from endothelial dysfunction to plaque rupture. Traditional biomarkers such as C-reactive protein (CRP) and neutrophil-to-lymphocyte ratio (NLR) have been widely used to reflect systemic inflammation; however, their predictive value remains limited when considered alone. Recently, the Systemic Immune-Inflammation Index (SII)—calculated as platelet count × neutrophil count / lymphocyte count—has emerged as a novel and reliable biomarker that integrates three key components of the immune and inflammatory response, providing a more comprehensive assessment of vascular inflammation.

Conclusion: Accumulating evidence indicates that a high SII is significantly associated with greater severity and complexity of coronary lesions, as reflected by higher SYNTAX scores, and may predict adverse cardiovascular outcomes in patients with CAD. Owing to its simplicity, cost-effectiveness, and availability in routine blood tests, SII could serve as a valuable adjunctive tool for early risk stratification and prognostic evaluation in coronary artery disease.

Keywords: Systemic Immune-Inflammation Index, Coronary Artery Disease, SYNTAX score, Inflammation, Biomarkers.

Introduction:

From tumor start to tumor metastasis, the cardiovascular inflammatory response is a key factor in determining the course of tumor development. Peripheral blood-derived inflammatory-related peripheral cells (neutrophils, lymphocytes, and platelets) were substantially linked to tumor growth in a number of tumor types [1].

Furthermore, other combinations of these factors have been used to produce inflammatory indices, such as the neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR), which have been studied as potential predictive markers for a variety of malignant solid tumors. Recently, a new inflammatory index called the SII—which is defined as SII = P*N/L, where P, N, and L are the peripheral platelet, neutrophil, and lymphocyte counts—was studied as a prognostic indicator for a number of cancers [2].

Through a variety of processes and pathways, inflammation contributes to the pathophysiology of cancer, including angiogenesis, metastasis, and proliferation. Numerous serum systemic inflammatory response markers, including the NLR, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio, have been shown in recent research to be useful as clinical prognostic indicators for a variety of cancer types [1].

Furthermore, it has been discovered that a number of inflammatory markers, including as CRP, PLT, and NLR, are connected to the prevalence of acute renal injury brought on by contrast [3].

Individual parameters alone, however, may cause these biomarkers to become unstable and are frequently affected by additional confounding variables [4]. SII provides a comprehensive picture of a patient's inflammatory and immunological condition simultaneously, based on three inflammatory biomarkers: PLT, neutrophils, and lymphocytes [5].

The SII index has been widely used to assess the prognosis and forecast the incidence of a number of malignancies. SII was also linked to the clinical prognosis of CAD patients following coronary intervention, according to recent research. The relationship between SII and the CI-AKI risk is still unknown, but [6].

SII = P*N/L, where P, N, and L were the peripheral platelet, neutrophil, and lymphocyte counts, is the definition of the unique inflammatory index, the SII, as previously discussed [7].

SII is utilized to predict clinical outcomes in patients with coronary artery disease [8], according to Ya-Ling et al., 2020.

Innate and adaptive immune responses, which are primarily made up of lymphocytes, neutrophils, monocytes, and macrophages, have distinct roles in the development of atherosclerosis, according to scientific evidence. Atherogenesis is a major cause of most cardiovascular events, and both immunity and inflammation play critical roles in this process. Research has demonstrated that platelet adherence to artery walls promotes leukocyte recruitment and occurs before leukocyte infiltration of atherosclerotic plaque, which starts the atheroprogression process [9].

According to certain research, leukocytes that contribute to both systemic and local inflammation may be linked to the etiology of CVD. One study, for instance, discovered that the pattern of cellular activation at local inflammatory sites in atherosclerotic plaques contrasted with systemic changes in the activity of polymorphonuclear cells, specifically neutrophils and T lymphocytes, in patients with acute coronary syndrome. This suggests that both local and systemic inflammatory processes may be involved in the pathophysiology of acute coronary syndrome [10].

Further supporting evidence for the role of systemic inflammation in the pathophysiology of atherothrombosis was provided by a different study that detailed how total white blood cell count and macrophage density could predict the presence of thin-cap fibroatheromas in patients undergoing coronary angiography, both separately and in combination [8].

Even though their potentially conflicting activities may not be fully understood, examining neutrophils, platelets, and lymphocytes collectively may help shed light on how these three cell types interact in the pathophysiology of cardiovascular disease (CVD) because the SII integrates signals from these three cell types. Furthermore, investigating how these blood components interact to cause CVD in people who have never had the condition before may provide important new information [7].

Role of Platelets

Through their direct interactions with leucocytes and endothelial cells, as well as the release of numerous proteins and lipids, including thromboxane (TX)A2, adenosine diphosphate (ADP), and a variety of angiogenic and growth factors, stored in dense granules and α-granules, platelets play a key role in inflammation. Leucocyte recruitment into various tissues and phenotypic changes in stromal cells are caused by these platelet actions, which set off autocrine and paracrine activation processes. These changes aid in the development of various disease states, including intestinal inflammation, cancer, and atherosclerosis and atherothrombosis [7].

Platelet-induced signals can produce abnormal expression of cyclooxygenase (COX)-2 and increased production of prostanoids, primarily prostaglandin (PG)E2, which can lead to pro-inflammatory and malignant phenotypes in other cells. In addition to cardiovascular illness, intestinal tumorigenesis and inflammatory diseases have also been linked to increased platelet activation [11].

Additionally, clinical research has demonstrated that aspirin, an antiplatelet medication, lowers the risk of colon cancer and vascular events. All of these pieces of data point to the possibility that colorectal cancer and

atherothrombosis may be caused by the same mechanism, which is platelet activation in response to endothelium (in atherothrombosis and tumorigenesis) and epithelial (in tumorigenesis) damage.To gain a conclusive mechanistic demonstration of the platelet-mediated theory of colon tumorigenesis, a significant amount of translational medicine research is required [9].

An key connection between tissue injury or malfunction and the inflammatory response is represented by platelets, which at first work to repair the damage but can lead to a variety of pathological diseases if platelet activation is not managed. What happens in the arterial wall is the most well-known illustration of the role platelets play in inflammation. Circulating leucocytes are drawn in, activated, transmigrate, and form foam cells as a result of platelet adherence to injured or dysfunctional endothelium. Therefore, the inflammatory underpinning for plaque development may be provided by platelets [9].

At the locations where plaque rupture occurs in a major arterial vessel (such as a coronary artery), platelets are also activated and contribute to thrombosis, which physically blocks the vessel. TX A2, a strong pro-aggregatory and vasoconstrictor mediator that is essential for the development and maintenance of an intraluminal cardiac thrombus, is produced and released by platelets in this situation [12].

Platelets produce TXA2, a lipid autacoid that is a member of the prostanoids family, from arachidonic acid (AA) through the simultaneous action of TXA2 synthase (TXAS) and COX-1. The constant discovery that individuals with unstable angina who take low doses of the antiplatelet drug aspirin had a 50% lower risk of myocardial infarction or death from vascular causes suggests the role of TXA2. Low-dose aspirin really works by selectively acetylating the hydroxyl group of one serine residue at position 529 (Ser529) inside the COX active region of COX-1, which results in an irreversible reduction of platelet COX-1 activity [13].

The ability of platelets to produce COX-2-dependent prostanoids in vascular, inflammatory, stromal, and tumor cells will be highlighted among the many mechanisms they trigger. This is a crucial mechanism for inducing the intricate biological cascade of molecular and cellular signals that maintain homeostatic functions and mediate pathogenic responses. Actually, the more significant source of prostanoid production in inflammation and proliferative disorders is COX-2, which is triggered by inflammatory stimuli, hormones, and growth factors [11].

However, the production of autoregulatory and homeostatic prostanoids is facilitated by COX-2, which is constitutively expressed in endothelial cells in vivo 12. This explains why non-steroidal anti-inflammatory drugs (NSAIDs) selective for COX-2 (called coxibs) and other conventional NSAIDs have been found to increase cardiovascular risks. These drugs affect the endothelial biosynthesis of COX-2-dependent prostanoids while leaving platelet biosynthesis of TXA2 unaffected [9].

Megakaryocyte-derived messenger RNA (mRNA) and the translational machinery required for protein synthesis are found in platelets. Between 3000 and 6000 transcripts make up the platelet transcriptome. According to certain research, platelets may convert mRNAs into proteins involved in inflammation and hemostasis. The occurrence of de novo COX-1 synthesis in platelets is supported by our demonstration that COX-1 mRNA is easily identified in resting platelets and that [35S]-methionine is integrated into COX-1 protein following stimulation. Aspirin's ability to completely and consistently decrease TXA2 production, which is essential for cardioprotection, may be hampered by this mechanism [14].

High amounts of microRNAs (miRNAs) are also expressed by normal human platelets. miRNAs are tiny RNA molecules that either suppress translation or degrade mRNA to alter the production of proteins. They have been demonstrated to have significant roles in a number of pathological (like cancer) and physiological (like hematopoiesis, including megakaryocytopoiesis) processes [15].

Pre-miRNA can be converted into mature miRNA by the miRNA processing machinery found in human platelets, which includes Dicer, TAR RNA-binding protein 2, and Ago2. Platelet miRNAs have plenty of chance to control platelet activity because miRNAs can target a wide variety of different mRNAs. Platelet-mediated transport of miRNAs to other cellular locations is possible since miRNAs can be released through vesicle secretion [16].

α-granules are cytoplasmic granules found in platelets that contain several proteins. Numerous proteins are present in them, such as growth factors (PDGF, bFGF, SDF1), proteases (MMP2, MMP9), necrotic factors (TNF), angiogenic factors (angiogenin, VEGF), anti-angiogenic factors (angiostatin, PF4), hemostatic factors (factor V, vWF, fibrinogen), and other cytokines. These mediators can be variably secreted from various populations of α-granules. Granules carrying pro-angiogenic factors are released with selective activation of the protease-activated receptor (PAR)-1, while granules containing anti-angiogenic factors are released upon selective activation of the PAR-4 receptor [17].

Glycoprotein (GP) receptors are among the functionally specialized proteins found in the platelet's plasma membrane and glycocalyx. These proteins react with enzymes, other proteins, cations, and nucleotides in the environment to help activate platelets. These receptors are also involved in the adhesion of platelets to extracellular matrix (ECM) components, other platelets, and other cell types, including endothelial, leucocyte, and tumor cells. Previous publications and reports have provided in-depth analyses of the biology of platelet receptors in both health and sickness [18].

TXA2 is produced and released when platelets are activated by strong agonists like collagen or thrombin. It functions by connecting with TXA2 receptors, also known as TP. Through alternative splicing, two isoforms of the human TP (TPα, TPβ) are produced; they differ solely in their C-terminal tails. Whereas TPβ exhibits a more restricted tissue distribution, TPα is widely expressed in many tissues. Even if they have leftover β isoform RNA, platelets show substantial levels of the α isoform but not the β isoform protein. Phospholipase C is activated by both TP isoforms when they couple with the G protein type, Gq (Gq, G11, G15, G16). Additionally, TPβ inhibits adenylyl cyclase, while TPα increases it. Additionally, the receptor has the ability to couple with the G13 (G12, G13) families, which activates the small G protein Rho's guanine nucleotide exchange factor [19].

Its contribution to the release reaction, which releases enough ADP from dense granules to account for the positive feedback mechanism involved in the formation of platelet aggregate, is notable among the platelet reactions caused by TXA2 [20].

Thus, aspirin's ability to reduce TXA2 synthesis is linked to its ability to prevent ADP-induced second-phase platelet aggregation. When ADP is produced, it coordinately activates the purinergic receptors P2Y1 and P2Y12, which are G protein-coupled receptors [18].

Through their autocrine and/or paracrine actions, TXA2 and ADP increase the platelet response. In actuality, these secondary platelet agonists engage with particular receptors expressed in the same cell or/and in nearby platelets after being released from platelets, drawing them into an expanding thrombus. In platelets, activation of TP, ADP receptor (P2Y12), thrombin, and collagen receptors causes vascular smooth muscle cells (VSMCs), endothelial cells, leucocytes, and stromal cells to release α-granule content, which is rich in angiogenic proteins, in addition to the initial activation signal spreading to neighboring platelets [18].

It is noteworthy that platelet activation and α-granule release are inhibited by endothelial prostacyclin (PGI2), which is mostly produced by COX-2 activity [21].

Role of Neutrophils and Oxidative Stress

Numerous factors affect neutrophilia and lymphocytopenia, which are immune system reactions to systemic inflammation, injury, and stress [22]. By phagocytosing and producing cytokines and mediators, neutrophils function as forerunners of the innate immune response. They help regulate adaptive immunity and serve as the primary effectors during the early hyperdynamic phase of infection [23]. Increased neutrophil counts can result from a number of conditions, including infection, acute stroke, myocardial infarction, atherosclerosis, severe trauma, burns, major surgery, and any circumstance involving tissue damage that triggers SIRS [24].

Neutrophilia during systemic inflammation is caused by stem cell stimulation by growth factors such G-CSF, neutrophil demargination, and inhibited neutrophil apoptosis [25]. Malignancy, severe trauma, major surgery,

severe sepsis, and systemic inflammation are all associated with lymphocytopenia, a substantial reduction in the number of circulating lymphocytes. Numerous studies have examined this decline in lymphocytes, which is a sign of weakened cell-mediated immunity. For example, neuroendocrine stress and tissue damage change the T4/T8 lymphocyte ratio in situations like repeated trauma and extensive surgery, resulting in lymphocytopenia within 6 hours that lasts for 2–7 days [11].

The processes that cause lymphopenia also include increased apoptosis caused by tumor-related cytokines (especially interleukin [IL-10] and tumor necrosis factor beta) and the margination and redistribution of lymphocytes within the lymphatic system. Additionally, lymphocytopenia is caused by ischemia-reperfusion injury (myocardial infarction, for example) and elevated pro-inflammatory cytokines (acute pancreatitis, for example) [26].

This phenomena is made more complex and intriguing by the simultaneous but opposing changes in neutrophil and lymphocyte counts, which indicate a multifactorial dynamic response impacted by immunologic, neuroendocrine, humoral, and biological components. Furthermore, neutrophil and lymphocyte counts alter early (less than 6 hours) after acute physiological stress, making them earlier markers than other laboratory parameters (such as CRP and white blood cell count) [27].

Despite prior research examining the distinct roles of neutrophil and lymphocyte numbers in the clinical severity of the systemic inflammatory response, Zahorec identified the neutrophil-lymphocyte ratio (NLR) in 2001. The ratio of neutrophil to lymphocyte counts (in absolute and/or relative percentage values), or NLR, has been suggested as a straightforward, accurate, and economical way to measure the severity of a number of stressful events in critically ill patients, including peritonitis, abdominal sepsis, complicated postoperative periods, severe sepsis, and septic shock. According to further studies, the NLR is a more accurate indicator of patient survival than either neutrophil or lymphocyte counts by itself [2].

The median NLR appears to be 1.65 (range 1.2–2.15) when looking at the reported normal values of NLR in healthy people of various races around the world. Although the initial study defined NLR values below 5 as normal, other diseases (such as cancer, sepsis, and cardiovascular disorders) have been found to have varied cutoff values, and there is still disagreement over a single pathological value in this area [28].

According to a recent meta-analysis of 11,564 sepsis patients, a greater NLR was independently linked to a worse clinical prognosis for sepsis patients (mean HR = 1.75; 95% CI = 1.56–1.97). Compared to survivors, nonsurvivors had a considerably higher NLR (mean HR = 1.18; 95% CI = 0.42–1.94) [2].

According to most of the research that is currently available, an NLR of ≥5 is a reliable indication of sepsis, and values more than 10 are significant in septic shock [29]. Additionally, it has been proposed that 28-day mortality is linked to both high and lower-than-expected NLR values (0.1–0.7) [30]. Although NLR has been proposed as a more accurate and economical sepsis marker than CRP, its superiority over procalcitonin has not been proven [31].

Numerous studies have been conducted in the literature on the connection between NLR and pneumonia/respiratory failure. In community-acquired pneumonia, NLR has demonstrated a high predictive value for both short- and long-term mortality, intensive care unit admission, and rehospitalization [32].

High NLR at admission was linked to greater overall mortality in both STEMI and NSTEMI patients (OR = 4.60; 95% CI: 2.84–7.45, and OR = 6.41; 95% CI: 2.65–15.50, respectively) compared to low NLR, according to a major meta-analysis comprising over 16,000 patients. STEMI patients with elevated initial NLR had a greater MACE risk (OR = 3.71; 95% CI: 2.67–5.17) [33].

High NLR has been linked to an increased risk of venous thromboembolism (VTE) in cancer patients (HR = 1.2; 95% CI = 1.0–1.4). More recently, it has been demonstrated that NLR is linked to an increased risk of VTE in non-cancer patients, including cerebral venous thrombosis (CVT), deep vein thrombosis (DVT), and pulmonary embolism [PE]. It can also predict recurrence, though it might not be enough to differentiate between the subtypes [32].

Oxidative stress states that a lot of cellular functions are controlled by reactions that involve the transfer of electrons between molecules, changing the redox state (the equilibrium between reduced and oxidized forms of electron donors and acceptors). Cellular and extracellular redox buffering systems, which comprise protein- and small-molecule-based buffers including the redox couples cysteine/cysteine, oxidized/reduced thioredoxin, and GSH/GSSG (glutathione-glutathione disulfide), are responsible for maintaining redox homeostasis [34].

Essential antioxidant enzymes such as superoxide dismutase, catalase, and the selenoproteins glutathione peroxidase and thioredoxin reductase, along with non-enzymatic antioxidants like α-tocopherol (vitamin E), ascorbate (vitamin C), β-carotene, and flavonoids, keep these buffering systems in balance [35].

Every time an imbalance between reductants (electron donors) and oxidants (electron acceptors) arises, redox homeostasis is disrupted. This imbalance can lead to either a reductive stress, where the redox potential becomes more negative, or an oxidative stress, where the redox potential becomes more positive. The latter is by far the most prevalent type of redox imbalance in biological systems [36].

Oxidative stress, which is best described as "an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage," is caused by the production of different oxidizing chemical species in excess of the cellular reducing capacities [37].

Free radicals, which are molecules with one or more unpaired electrons in their molecular orbitals that stabilize by stealing electrons from nearby molecules, are the most common type of oxidant species. Because of their extremely positive redox potential, some non-radical species, such as hydrogen peroxide or peroxynitrite, also function as potent electron acceptors. According to (Figure 1) [38], the reactive oxygen species (ROS) and the reactive nitrogen species (RNS) are the two primary families of pertinent oxidants in biology.

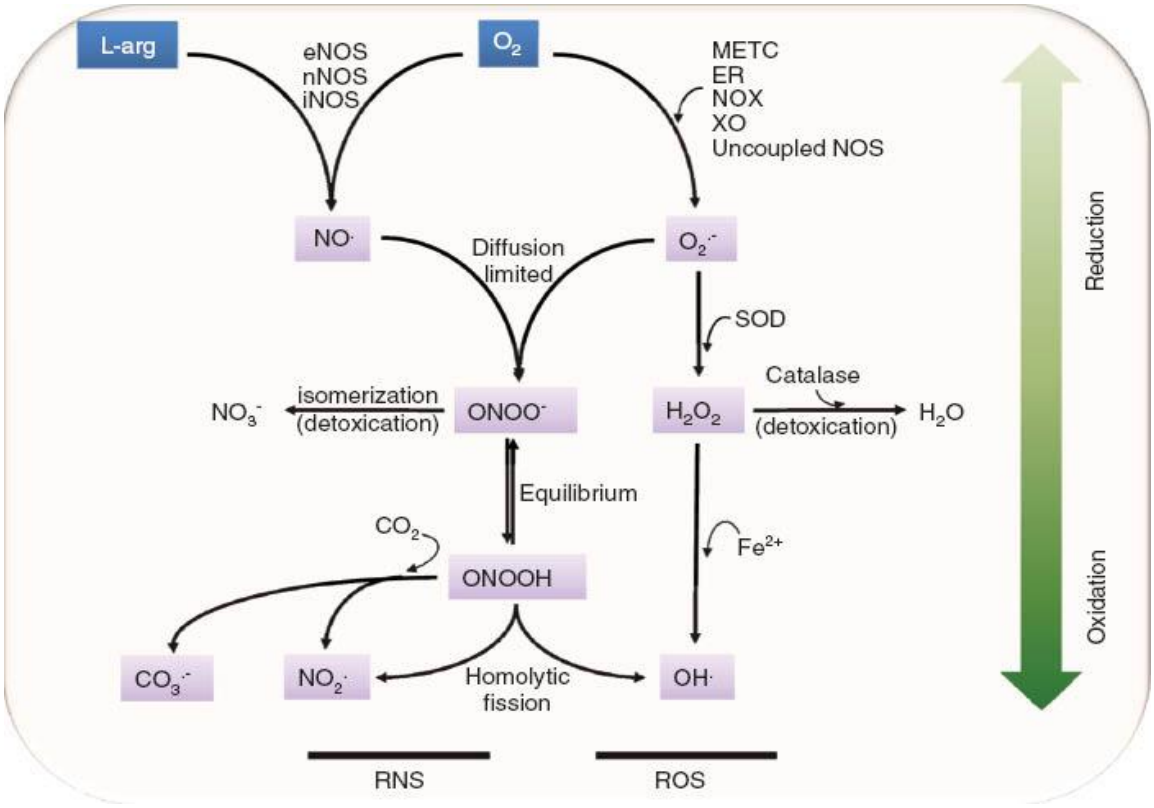

Figure 1: Molecular pathways of RNS and ROS generation [39].

ROS family; The main ROS molecule produced in biological systems by the univalent reduction of molecular oxygen is the superoxide anion radical (O2.-). Secondary ROS are produced by enzymatic and metal-catalyzed (Fenton) processes, which result in the addition of a second and third electron, respectively, producing hydrogen peroxide (H2O2) and the hydroxyl radical OH. Additionally, after its spontaneous interaction with nitric oxide, O2.-promotes the development of the strong oxidant and nitrating species peroxynitrite [40].

Due to the "leakage" of electrons from the electron transport chain, primarily at the ubiquinone binding sites of complex I and complex III, which results in the one-electron reduction of oxygen, the mitochondria continuously produce O2.-. Thus, as a byproduct of mitochondrial respiration, about 2% of the oxygen consumed under normal conditions is converted to O2.-. The mitochondrial enzyme manganese superoxide dismutase scavenges O2.- quickly, preventing oxidative damage [41].

However, under a number of pathological situations, such as inflammation or hypoxia, which encourage damage to electron transport within the mitochondrial respiratory chain, the production of ROS may rise noticeably [42].

In addition to mitochondria, another organelle that contributes to the production of ROS in cells is the endoplasmic reticulum (ER). Through the creation of disulfide bonds inside proteins, which are facilitated by the enzymes oxidoreductin 1 and protein disulfide isomerase, and the transfer of electrons to molecular oxygen, which results in H2O2, ER facilitates protein folding. When the ER is under stress (caused, for example, by inflammatory cytokines or elevated glucose levels), the accumulation of misfolded proteins within the ER sets off a defense mechanism known as the unfolded protein response, which is linked to a rise in ER-dependent ROS production [43].

The several isoforms of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), which is found in almost all cell types and is structurally made up of a core catalytic subunit and several regulatory subunits that control the enzyme's spatial organization, membrane location, subcellular expression, and activation, are the main enzyme systems whose activity also affects the production of O2 [44].

Numerous physiological (such as vascular tone and oxygen sensing) and cellular (such as differentiation, proliferation, and migration) activities are regulated by ROS generated by NOXs. When NOX is overactivated in response to a variety of stimuli, including hormones, growth factors, angiotensin II, hyperglycemia, and—most importantly—inflammatory cytokines like interleukin (IL)-1β and TNFα, excess ROS generation and oxidative stress result. Furthermore, during the so-called oxidative burst, activated neutrophils and macrophages generate a lot of reactive oxygen species (ROS) by activating NOX2. This process is crucial for getting rid of invasive pathogens, but it can also cause serious tissue damage in sterile inflammatory conditions linked to phagoyct activation [45].

RNS family; The free radical NO, the parent molecule of all RNS, interacts with metals and other free radicals to modify the biological activity of numerous proteins by S-nitrosylating cysteine residues. Under physiological conditions, NO. serves as a crucial cellular messenger and cytoprotective species [46].

The terms "nitroxidative stress" and "nitrative stress" are commonly used to describe the effects of excessive peroxynitrite formation in a biological system, while "nitrosative stress" refers to the effects of increased NO production [47]. This is analogous to the term "oxidative stress," which is associated with excessive ROS formation.

Role of lymphocytes and Immune Regulation

The host immune response, particularly an amplified lymphocytic reactivity, has recently come into focus of research due to the efficacy of checkpoint inhibitors in a wide range of tumors in recent years [48].

Tumor regression following immune checkpoint blockage was dependent on the presence of preexisting cytotoxic T lymphocyte cells in the tumor microenvironment, which can target cancer cells by identifying aberrantly produced neoantigens [49]. Hematoxylin-eosin (H&E)-stained sections can currently be used to evaluate the tumor immune response in relation to lymphocytic infiltrations based on the morphological

features of cells, which is a first practical and economical method. In recent years, a number of studies have validated the prognostic significance of tumor infiltrating lymphocytes (TILs) in a variety of malignancies [50].

Based on platelet, neutrophil, and lymphocyte counts, the SII was initially described by Muzaffer et al. in 2024. In comparison to single-parameter markers like the NLR or the PLR, further studies have shown that the SII has a higher predictive value for malignant tumors [51].

Role of Systemic Immune Inflammation Index in Coronary Artery Disease

Platelet × neutrophil/lymphocyte count, or SII, is a systemic immune-inflammation index that has recently been identified as an integrated biomarker that reflects both immune and inflammatory status. When evaluating systemic inflammation in coronary artery disease (CAD), it is thought to be more thorough than individual indices like NLR or PLR [52].

The degree and severity of coronary atherosclerosis have been shown to positively correlate with SII. Higher SYNTAX scores and more complicated lesions were associated with elevated SII values, suggesting that systemic inflammation directly contributes to the development of CAD [53].

It has been demonstrated that a high SII can more accurately predict major adverse cardiovascular events (MACE) after percutaneous coronary intervention than a number of conventional indicators, including CRP and NLR. In risk stratification following coronary revascularization, this emphasizes its prognostic potential [54].

SII is a useful and affordable biomarker that can be widely used in clinical practice, especially in places with low resources, because it can be obtained from a standard complete blood count (CBC) [55].

According to sex-specific research, men and women may have different associations between SII and CAD risk, which could be due to variations in immunological responses, platelet activity, and hormonal control [56].

SII levels in patients with acute coronary syndromes increase significantly at presentation and then progressively decline following stabilization, coinciding with shifts in inflammatory cytokines and troponin. Its function as a measure of persistent vascular inflammation is supported by this dynamic tendency [57].

The prognostic usefulness of SII for both cardiovascular and all-cause mortality has been validated by meta-analyses combining several trials, which imply that it represents chronic systemic inflammatory burden rather than only acute inflammatory episodes [58].

The trio of neutrophil-driven oxidative stress, excessive platelet activation, and lymphocyte suppression that promote endothelial dysfunction, plaque instability, and thrombosis is mechanistically mirrored by increased SII [59].

The inflammatory-metabolic relationship in the pathophysiology of CAD is further supported by the SII's evaluation in patients with diabetes and metabolic syndrome, which revealed a high correlation with insulin resistance and subclinical atherosclerosis [60].

SII may be incorporated into future clinical models in addition to conventional risk factors to enhance the early identification of individuals with high-risk CAD. To ascertain if therapeutic manipulation of SII can enhance cardiovascular outcomes, prospective randomized investigations are necessary [61].

Conclusion: A growing body of research suggests that a high SII may predict worse cardiovascular outcomes in CAD patients and is substantially linked to more severe and complex coronary lesions, as shown by higher SYNTAX scores. SII may be a useful supplementary tool for early risk stratification and prognostic assessment in coronary artery disease due to its affordability, convenience of use, and availability in standard blood tests. To confirm its predictive function and investigate its possible incorporation into clinical risk assessment models, more prospective research is necessary.

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