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Review

Conventional and Emerging Hematological Inflammatory Indices in Metabolic Syndrome: Narrative Review of Clinical Significance and Response to Bariatric Surgery

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Abstract

Background: Metabolic syndrome (MetS) is associated with chronic low-grade systemic inflammation. Complete blood count-derived inflammatory indices and biochemical ratios have emerged as accessible, low-cost markers of inflammation and potential indicators of cardiometabolic risk. **Objective**: This narrative review examined the clinical relevance of hematological inflammatory indices in MetS, focusing on the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune-inflammation value (PIV), as well as the uric acid-to-HDL cholesterol ratio (UHR) and changes following bariatric surgery (BS). **Methods**: A narrative literature review was conducted using PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar, from database inception to September 2026. The review addressed the links between obesity, inflammation, and MetS, the associations of these markers with cardiometabolic abnormalities, and their potential changes following BS. **Results**: NLR showed the most consistent associations with MetS, insulin resistance, and cardiometabolic risk. Evidence for PLR was less consistent, while MLR remained comparatively underinvestigated. Higher SII values were associated with obesity, MetS, hypertension, and glycemic abnormalities, whereas SIRI was linked to cardiovascular risk and adverse cardiometabolic profiles. Elevated PIV was also associated with obesity, diabetes, MetS, and insulin resistance. UHR was associated with MetS, insulin resistance, and other cardiometabolic abnormalities, although its discriminatory performance and clinical applicability remain limited. Following BS, changes in

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hematological inflammatory indices have been reported alongside weight loss and improvements in metabolic and inflammatory profiles; however, evidence regarding postoperative changes in SII, SIRI, and particularly PIV remains limited. **Conclusions**: Hematological inflammatory indices and biochemical ratios may complement cardiometabolic assessment, but their associations with MetS vary across markers and populations. The lack of validated cutoffs and established incremental predictive value limits their current clinical application. Prospective studies are needed to establish their prognostic value and clinical utility.

Keywords: obesity; metabolic syndrome; inflammation; hematological biomarkers; bariatric surgery

1. Introduction

Metabolic syndrome (MetS) is a clinical condition of major epidemiological and cardiometabolic relevance, associated with an increased risk of type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and premature mortality [1]. Characterized by the coexistence of abdominal obesity, insulin resistance, hypertension, hyperglycemia, and atherogenic dyslipidemia, MetS is no longer regarded solely as a clustering of cardiometabolic risk factors but is increasingly recognized as a systemic condition in which inflammatory mechanisms play a relevant role in its pathophysiology [1,2].

Over the past decades, obesity has reached epidemic proportions across different regions of the world. Estimates from the Global Burden of Disease indicate that approximately 2.11 billion adults were living with overweight or obesity in 2021, with projections suggesting that this number could reach approximately 3.8 billion by 2050, representing more than half of the global adult population [2]. In parallel with the increasing prevalence of obesity, MetS has become increasingly prevalent worldwide. It is estimated to affect approximately one-quarter of the global adult population, although prevalence rates vary according to population characteristics and the diagnostic criteria applied [3].

MetS is commonly defined using criteria established by the National Cholesterol Education Program Adult Treatment Panel III and the International Diabetes Federation, as well as the harmonized definition proposed in 2009. These definitions consider central obesity, elevated blood pressure, increased fasting glucose, elevated triglycerides, and reduced high-density lipoprotein cholesterol (HDL-C). Under the harmonized criteria, MetS is diagnosed when at least three of these five components are present, whereas the original International Diabetes Federation definition requires central obesity, defined according to population-specific waist circumference thresholds, plus at least two additional components. Differences in diagnostic criteria, particularly regarding the requirement for central obesity and waist circumference cutoffs, may influence case classification and prevalence estimates, thereby contributing to heterogeneity and limiting direct comparisons across studies [4,5].

In this context, chronic low-grade inflammation, also referred to as metaflammation, has emerged as an important mechanism underlying the development and progression of the metabolic abnormalities associated with MetS. Visceral adipose tissue plays a central role in this process by functioning as a metabolically active endocrine and immunological organ capable of secreting adipokines and pro-inflammatory cytokines that contribute to insulin resistance, endothelial dysfunction, and the development of atherogenic abnormalities. Thus, the interplay among adipose tissue expansion, immune activation, and metabolic dysfunction promotes and perpetuates a persistent state of systemic inflammation [6,7].

The inflammatory nature of MetS has been increasingly documented in clinical studies. In patients with T2DM, those with MetS exhibit significantly higher leukocyte counts and C-reactive protein levels than those without the syndrome, while even moderate weight gain

has been associated with the activation of inflammatory pathways, highlighting the link between adiposity and systemic inflammation [8,9]. Beyond these metabolic associations, higher composite inflammatory scores have also been linked to increased all-cause and cardiovascular mortality in longitudinal analyses of adults with MetS from the National Health and Nutrition Examination Survey [9]. Collectively, these findings underscore the clinical relevance of systemic inflammation in MetS and the need for accessible tools to assess inflammatory status in this population [8,9].

The assessment of this inflammatory process has attracted increasing interest in research on MetS. Traditionally used biomarkers, such as high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), provide relevant information on inflammatory activity; however, their use may be limited in certain settings by availability, cost, and the requirement for specific laboratory assays. In contrast, parameters routinely obtained from complete blood counts have enabled the development of low-cost and widely available inflammatory indices, thereby increasing interest in their potential application for assessing systemic inflammation associated with cardiometabolic abnormalities [10,11].

Among these indices, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) have been widely investigated, along with composite inflammatory indices such as the systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune-inflammation value (PIV). These parameters integrate different components of the immune and inflammatory responses and have been investigated in relation to obesity, visceral adiposity, insulin resistance, hypertension, and cardiovascular risk [10,12].

Recent evidence indicates associations between elevated levels of these indices and metabolic abnormalities related to MetS. A meta-analysis involving more than 70,000 individuals identified higher NLR values among individuals with MetS and reported an association between elevated NLR levels and a greater risk of developing the syndrome [13]. Similarly, studies examining SII, SIRI, and PIV have investigated their relationships with obesity, glycemic abnormalities, hypertension, insulin resistance, and cardiovascular outcomes [12,14,15]. However, the magnitude of these associations and their potential clinical applicability may vary according to the characteristics of the population studied, the diagnostic criteria adopted, and the cutoff values applied [13,15].

Furthermore, changes in these indices have been investigated in the context of weight loss and obesity treatment, particularly following bariatric surgery (BS). Reductions in visceral adiposity and the metabolic changes resulting from weight loss may modulate systemic inflammatory activity, prompting investigation of whether these parameters could serve as complementary markers of treatment-related changes in inflammatory status, a hypothesis that remains to be prospectively validated. Despite the growing body of evidence, further studies are needed to establish more consistent interpretative parameters, considering the influence of clinical and population characteristics on these indices and their relationship with conventional inflammatory biomarkers [16–20].

Against this background, the present narrative review aims to critically examine the clinical relevance of hematological inflammatory indices and biochemical ratios in the assessment of MetS, with particular emphasis on NLR, PLR, MLR, SII, SIRI, PIV, and the uric acid-to-HDL cholesterol ratio (UHR). The review first addresses the epidemiology of obesity and MetS and the pathophysiological mechanisms linking obesity, inflammation, and MetS. It then discusses the available evidence regarding the major hematological inflammatory indices and, finally, examines their potential applications in cardiometabolic risk assessment and in monitoring inflammatory changes associated with weight loss and BS.

2. Methodology

This narrative review was conducted to synthesize the current evidence on hematological inflammatory indices and biochemical ratios associated with MetS and their behavior in the context of BS. A comprehensive literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar between August and October 2026, with no restrictions on publication date. The search combined terms related to metabolic syndrome and its components ("metabolic syndrome", "insulin resistance", "obesity", "hypertension", and "dyslipidemia") with terms related to the biomarkers of interest, including "neutrophil-to-lymphocyte ratio", "platelet-to-lymphocyte ratio", "monocyte-to-lymphocyte ratio", "systemic immune-inflammation index", "systemic inflammation response index", "pan-immune-inflammation value", "uric acid-to-HDL cholesterol ratio", "uric acid-to-HDL ratio", "UHR", "inflammation", "complete blood count", and "bariatric surgery". No language restrictions were applied during the initial screening or full-text review, and articles published in any language were considered eligible for inclusion.

Studies were eligible for inclusion if they: (i) investigated at least one of the hematological inflammatory indices in adults with MetS, obesity, insulin resistance, or related cardiometabolic conditions; (ii) reported associations between these indices and metabolic, inflammatory, or cardiovascular outcomes; or (iii) evaluated postoperative changes in these indices following BS. Given the narrative scope of this review, no systematic protocol or PRISMA methodology was applied. Studies were selected and prioritized by relevance based on their direct assessment of MetS rather than isolated components, sample size, population representativeness, with priority given to population-based cohorts such as NHANES and the Multi-Ethnic Study of Atherosclerosis (MESA), methodological robustness, and recency. Reference lists of retrieved articles were also hand-searched to identify additional relevant studies. Data were synthesized descriptively, and the strength of evidence for each index was interpreted considering the consistency, magnitude, and methodological heterogeneity of the available findings. This approach is consistent with current recommendations for narrative reviews.

3. Epidemiology of Obesity and Metabolic Syndrome

Obesity is currently recognized as a chronic, complex, and multifactorial disease characterized by excessive adipose tissue accumulation that can impair health and increase the risk of several chronic noncommunicable diseases. Traditionally classified according to body mass index (BMI), with values between 25.0 and 29.9 kg/m^2 defining overweight and values ≥ 30 kg/m^2 defining obesity, the condition is now understood as a systemic disease whose health consequences extend beyond excess body weight alone [21,22].

Over the past decades, obesity has reached epidemic proportions worldwide. Data from the Global Burden of Disease study showed that approximately 2.11 billion adults were living with overweight or obesity in 2021, including 1.00 billion men and 1.11 billion women, with particularly pronounced increases observed in low- and middle-income countries. In 2022, approximately 43% of adults worldwide were living with overweight or obesity [23–25]. The global prevalence of obesity increased by more than 150% between 1990 and 2022, and projections indicate that approximately 3.8 billion adults could be living with overweight or obesity by 2050, representing more than half of the global adult population [2].

An important aspect of this epidemiological trend is the increasing prevalence of obesity among children and adolescents. Between 1990 and 2022, the prevalence of obesity in this age group increased approximately fourfold, whereas among adults it more than doubled. This trend increases the likelihood of obesity persisting into adulthood and

contributes to the earlier onset of chronic noncommunicable diseases, including T2DM and CVD [24,26].

In addition to the increasing prevalence observed over time and across different age groups, the distribution of obesity exhibits considerable heterogeneity across geographic regions and levels of socioeconomic development. Scientific evidence indicates a higher prevalence of obesity among individuals with lower educational attainment, older adults, and women. Obesity has also been associated with behavioral factors, including physical inactivity and unhealthy dietary patterns [25,27].

Low- and middle-income countries have experienced particularly rapid increases in obesity prevalence, while some regions, including the Middle East, North Africa, and Oceania, have reported prevalence rates exceeding 60% of the adult population. Furthermore, many developing countries face a double burden of malnutrition, characterized by the coexistence of undernutrition and obesity, a phenomenon closely associated with urbanization and transitions in dietary patterns and physical activity behaviors [2,21].

The increasing prevalence of obesity has major clinical implications, as excess adiposity is associated with the development of several chronic conditions, including T2DM, hypertension, dyslipidemia, and CVD, as well as certain types of cancer, musculoskeletal disorders, and respiratory conditions, particularly sleep-related breathing disorders [28]. Excess body weight therefore represents an important contributor to morbidity and premature mortality and imposes a substantial economic burden on healthcare systems, with global economic costs projected to exceed USD 4 trillion annually in the coming decades [21,29,30].

Within this context, MetS represents a condition of considerable clinical and epidemiological relevance. It is estimated that approximately one-quarter of the global adult population has MetS, although its prevalence varies substantially across countries, ethnic groups, and the diagnostic criteria applied. These epidemiological patterns underscore the importance of understanding the mechanisms underlying the development and progression of obesity and MetS, as well as identifying potential biomarkers associated with cardiometabolic risk [3,24].

4. Obesity, Inflammation, and Metabolic Syndrome: Pathophysiological Basis

4.1. Adipose Tissue Dysfunction and Metaflammation

Obesity should be understood as a complex systemic disease resulting from the interplay among genetic, neuroendocrine, metabolic, immunological, environmental, and behavioral factors that contribute to a chronic imbalance between energy intake and energy expenditure. Although obesity has traditionally been defined by a BMI ≥ 30 kg/m^2, disease severity is also closely related to body fat distribution and adipose tissue function. In particular, central obesity is more strongly associated with cardiometabolic complications than peripheral adiposity [22,31].

Accumulating scientific evidence over recent decades has demonstrated that metabolic inflammation, also referred to as metaflammation, plays a central role in the development and progression of the metabolic abnormalities that characterize MetS [28,32]. The major pathophysiological mechanisms underlying this process are illustrated in Figure 1.

This relationship is complex and bidirectional, as activation of the immune system may precede and directly contribute to the development of metabolic abnormalities. In genetically predisposed individuals exposed to environmental and lifestyle-related factors, such as excessive caloric intake, physical inactivity, and aging, persistent activation of inflammatory pathways may promote insulin resistance, endothelial dysfunction, and early atherosclerotic changes [7,33].

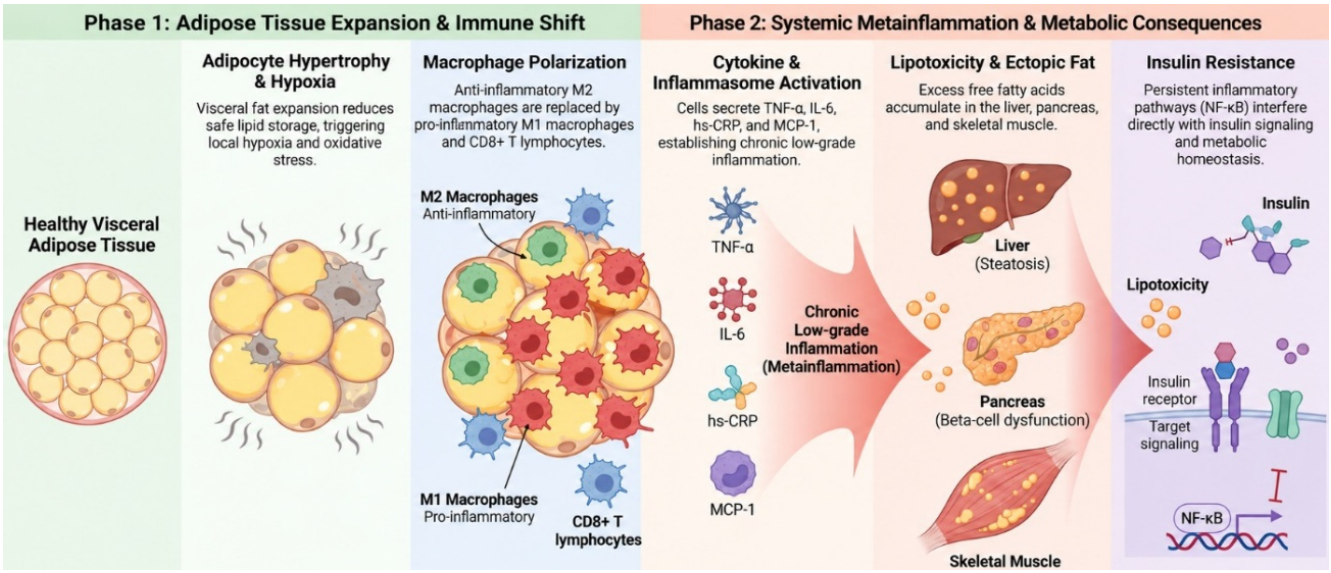

Figure 1. Pathophysiological mechanisms underlying adipose tissue dysfunction and obesity-associated metaflammation. The schema was generated with the assistance of Gemini Notebook. Abbreviations: TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; hs-CRP, high-sensitivity C-reactive protein; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor kappa B; M1, pro-inflammatory macrophages; M2, anti-inflammatory macrophages; CD8+, cluster of differentiation 8-positive T lymphocytes.

Adipose tissue, once regarded merely as an energy storage depot, is now recognized as a metabolically active endocrine and immunological organ capable of producing a wide range of bioactive mediators, including adipokines. Under physiological conditions, anti-inflammatory mediators such as adiponectin contribute to the maintenance of insulin sensitivity and metabolic homeostasis [6,34].

During the development of visceral obesity, excessive adipose tissue expansion, adipocyte hypertrophy, and impaired capacity for safe lipid storage occur. This microenvironment promotes local hypoxia, oxidative stress, and the recruitment of inflammatory cells, particularly pro-inflammatory macrophages. Obesity also alters the immune profile of adipose tissue, with a shift from predominantly anti-inflammatory macrophages (M2) toward a pro-inflammatory macrophage (M1) phenotype, accompanied by increased infiltration of Cluster of differentiation 8-positive (CD8+) T lymphocytes, neutrophils, and other immune cells involved in adipose tissue inflammation [32,35].

Activation of these immune cells promotes the sustained production of pro-inflammatory mediators, including TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1), contributing to the establishment of chronic low-grade systemic inflammation and increased circulating levels of inflammatory biomarkers such as hs-CRP. Persistent activation of inflammatory signaling pathways, particularly those involving nuclear factor kappa B (NF-κB) and the inflammasome, disrupts insulin signaling and thereby contributes to the development and progression of insulin resistance [6,36].

The inflammasome is an intracellular multiprotein complex involved in the activation and maturation of pro-inflammatory cytokines, particularly interleukin-1β (IL-1β) and interleukin-18 (IL-18). Excessive inflammasome activation in response to nutrient overload, lipid-derived signals, and cellular stress further amplifies systemic inflammation and aggravates the metabolic abnormalities associated with obesity and insulin resistance [6]. In addition, excess free fatty acids released from visceral adipose tissue exacerbate inflammatory and metabolic dysfunction through lipotoxic mechanisms, promoting ectopic lipid accumulation in organs such as the liver, pancreas, and skeletal muscle [10,36].

4.2. Insulin Resistance as an Inflammatory–Metabolic Link

Insulin resistance represents one of the major pathophysiological links among obesity, inflammation, and MetS. Under physiological conditions, insulin promotes glucose uptake by peripheral tissues and regulates energy metabolism. However, persistent exposure to pro-inflammatory cytokines can impair the appropriate phosphorylation of insulin receptor substrates, disrupting intracellular insulin signaling and reducing tissue responsiveness to insulin [10,36].

Consequently, compensatory hyperinsulinemia and impaired glucose tolerance may develop, ultimately contributing to the progression toward T2DM. In addition, hyperinsulinemia may promote renal sodium retention, sympathetic nervous system activation, and smooth vascular muscle proliferation, thereby contributing to the development of systemic arterial hypertension. Insulin resistance is also associated with abnormalities in lipid metabolism and blood pressure regulation, further contributing to the other components of MetS [34,37].

An imbalance in adipokine profiles further contributes to the persistence of metabolic dysfunction. Adiponectin, which exerts anti-inflammatory, anti-atherogenic, and insulin-sensitizing effects, is typically reduced in individuals with obesity and MetS. In contrast, circulating leptin and resistin concentrations are frequently increased and have been associated with pro-inflammatory signaling, impaired insulin sensitivity, and the maintenance of systemic inflammation [34,38]. The major mechanisms linking insulin resistance to its systemic metabolic and cardiovascular consequences are illustrated in Figure 2.

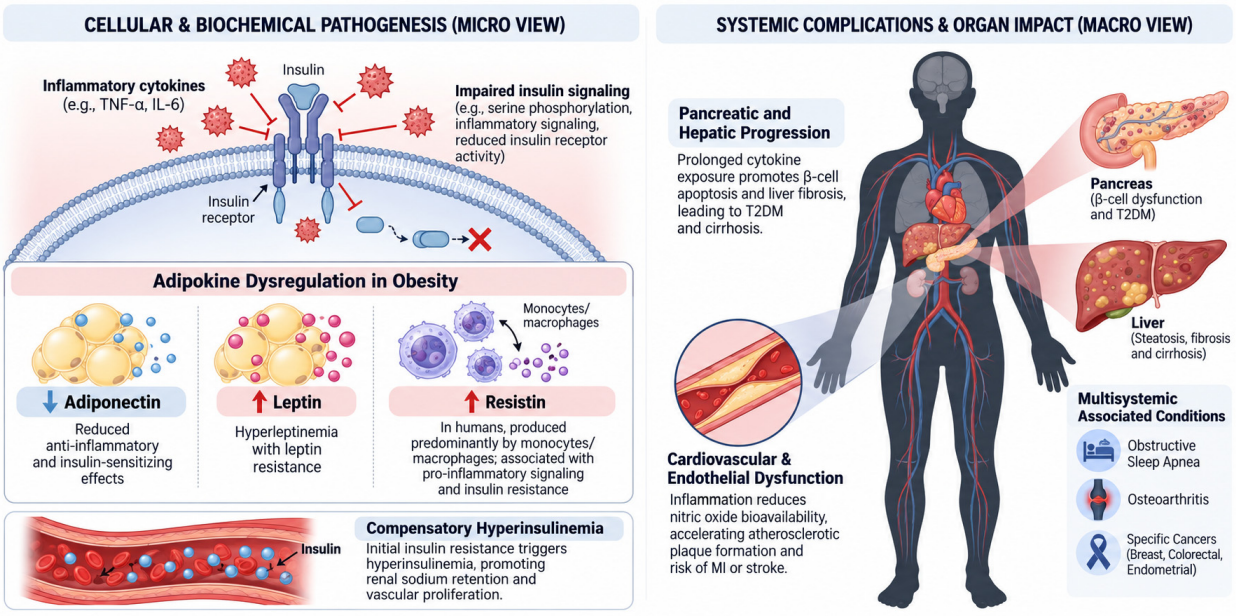

Figure 2. Cellular and systemic mechanisms associated with insulin resistance in obesity. The schema was generated with the assistance of Gemini Notebook. Legend: TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; T2DM, type 2 diabetes mellitus; MI, myocardial infarction.

Systemic inflammation also contributes to the progression of metabolic abnormalities and the development of T2DM. Prolonged exposure of pancreatic β-cells to pro-inflammatory cytokines impairs their secretory function and promotes apoptosis. Consequently, initially compensated insulin resistance may progressively evolve toward relative β-cell failure and persistent hyperglycemia [10,36].

Within the cardiovascular system, inflammation promotes endothelial dysfunction, reduces nitric oxide bioavailability, increases the expression of adhesion molecules, and facilitates the recruitment of inflammatory cells into the vascular wall. These processes

contribute to the initiation and progression of atherosclerotic plaques, thereby increasing the risk of coronary artery disease, myocardial infarction (MI), and stroke. Associations between increased BMI, visceral adiposity, and the incidence of cardiovascular events have also been reported, with CVD accounting for a substantial proportion of obesity-related mortality [11,39].

The relationship between chronic low-grade inflammation and MetS has also been investigated in patients with type 1 diabetes mellitus across different stages of diabetic kidney disease. In this context, hs-CRP levels increased with the number of MetS components, and the coexistence of MetS and elevated inflammation was associated with a higher risk of coronary artery disease among participants with preserved renal function [40].

In the liver, ectopic lipid deposition resulting from increased free fatty acid flux from visceral adipose tissue contributes to the development of metabolic dysfunction-associated steatotic liver disease (MASLD). Progression to metabolic dysfunction-associated steatohepatitis (MASH) involves inflammatory mechanisms and may ultimately lead to fibrosis, cirrhosis, and hepatocellular carcinoma. The liver also contributes to systemic inflammation through increased synthesis of CRP and other acute-phase proteins in response to inflammatory signaling [10,36].

Within the respiratory system, obesity is associated with obstructive sleep apnea, obesity hypoventilation syndrome, and pulmonary hypertension, conditions that may be associated with intermittent hypoxia and further amplification of systemic inflammatory responses. Obesity has also been associated with osteoarthritis, depression, anxiety, and several types of cancer, including postmenopausal breast, colorectal, and endometrial cancers, through complex mechanisms involving hyperinsulinemia, hormonal alterations, and persistent chronic inflammation [28,31].

4.3. Oxidative Stress, Immune Dysfunction, and Microbiota Alterations

Another relevant mechanism involved in the pathophysiology of MetS is oxidative stress. Excessive production of reactive oxygen species associated with obesity, hyperglycemia, and dyslipidemia promotes cellular damage and activates additional pro-inflammatory signaling pathways. Oxidative stress and inflammation are closely interconnected and mutually reinforcing processes that contribute to endothelial injury, vascular dysfunction, and the progression of atherosclerosis. The imbalance between oxidative and antioxidant mechanisms represents a key component of MetS pathophysiology and its associated cardiovascular complications [3,10]. The interplay among these mechanisms and their systemic consequences is illustrated in Figure 3.

The immune response is also substantially altered in MetS. Obesity induces changes in the immune profile of adipose tissue, characterized by increased infiltration of inflammatory cells and a predominance of pro-inflammatory phenotypes. Furthermore, excess adiposity and the metabolic abnormalities associated with MetS may induce structural changes in lymphoid organs, alter leukocyte distribution, and promote a shift toward pro-inflammatory immune phenotypes. Collectively, these alterations may impair appropriate immune responses, increase susceptibility to infections, and reduce vaccine responsiveness [35,41].

The gut microbiota also plays an important role in the relationship between inflammation and MetS. Alterations in its composition, commonly referred to as gut dysbiosis, may increase intestinal barrier permeability and facilitate the translocation of bacterial endotoxins into the systemic circulation. This process activates innate immune receptors and amplifies the production of pro-inflammatory cytokines. In addition, dysbiosis may alter the production of beneficial microbial metabolites, particularly short-chain fatty acids, thereby reducing their anti-inflammatory and metabolic regulatory effects and contributing to the development and progression of insulin resistance [10].

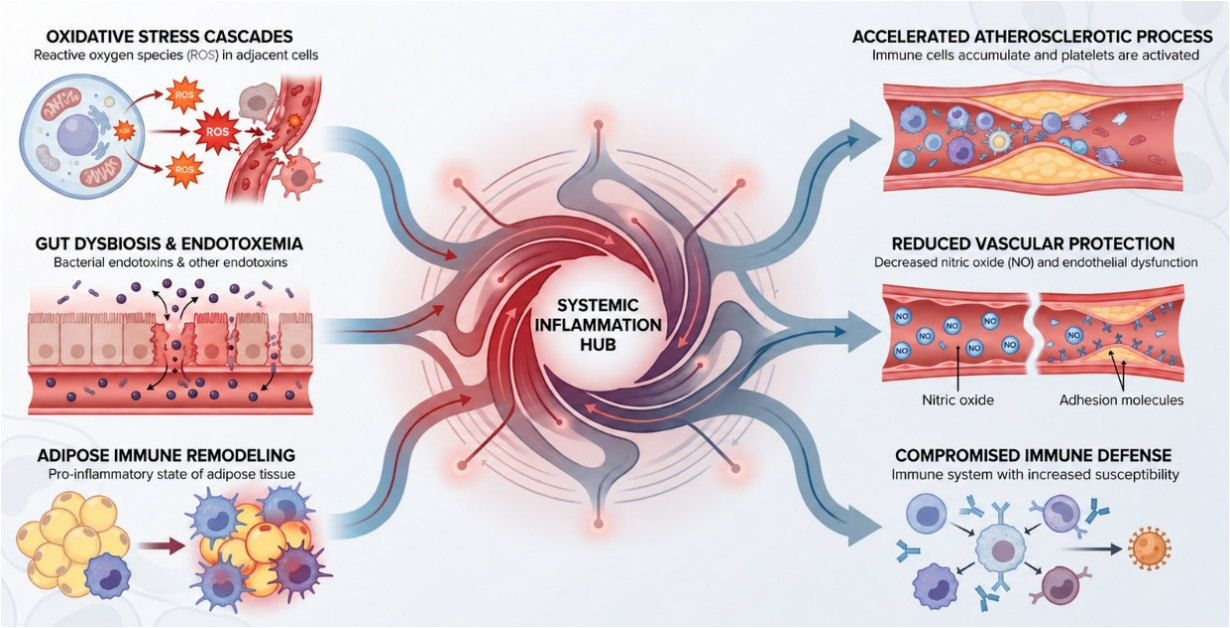

Figure 3. Mechanisms associated with oxidative stress, immune dysregulation, and gut microbiota alterations in metabolic syndrome and their systemic consequences. The schema was generated with the assistance of Gemini Notebook.

The interplay among inflammation, immune dysregulation, oxidative stress, and metabolic dysfunction has direct consequences for the cardiovascular system. Interactions between inflammatory cells and platelets contribute to monocyte recruitment to the vascular wall and accelerate atherogenesis, while pro-inflammatory cytokines, ROS, and lipid abnormalities reduce nitric oxide bioavailability and increase the expression of endothelial adhesion molecules [35].

Taken together, MetS can be understood as a systemic condition characterized by chronic low-grade inflammation, in which visceral obesity, insulin resistance, oxidative stress, immune dysregulation, and gut microbiota alterations interact through complex and interconnected pathways. Inflammation is therefore not merely a consequence or accompanying feature of MetS but represents a key pathophysiological mechanism involved in its development and progression [6,7].

5. Hematological Indices of Systemic Inflammation in Metabolic Syndrome

5.1. Conventional Hematological Markers and Inflammatory Ratios

Systemic inflammation associated with MetS can be assessed using various circulating biomarkers, among which hs-CRP, total leukocyte count, neutrophils, lymphocytes, and platelets are particularly relevant. Elevated levels or counts of these parameters have been associated with immune activation and cardiovascular risk, and a significant association between hs-CRP levels and the presence of MetS has been consistently reported [42–45]. Furthermore, studies have demonstrated that visceral adiposity is more closely associated with inflammatory markers than subcutaneous adiposity, with hs-CRP levels and leukocyte counts showing direct associations with visceral fat area and the visceral-to-subcutaneous fat ratio [37].

Inflammatory activation in MetS involves multiple immune cell populations. As described by Saltiel and Olefsky, obesity-associated inflammation involves the activation and recruitment of leukocytes, including monocytes, neutrophils, eosinophils, and T lymphocytes, accompanied by increased production of inflammatory mediators and endothelial dysfunc-

tion. Interactions between inflammatory cells and platelets also promote monocyte recruitment to the vascular wall, thereby contributing to the progression of atherosclerosis [35].

In this context, inflammatory ratios derived from routine complete blood count parameters have attracted increasing attention because of their simplicity, low cost, widespread availability, and potential clinical applicability. Among the most extensively investigated are the NLR, PLR, and MLR. These parameters integrate different cellular components of the inflammatory and immune responses and may provide complementary information beyond that obtained from conventional inflammatory biomarkers [46,47]. The major hematological ratios derived from complete blood count parameters and their corresponding cellular components are illustrated in Figure 4.

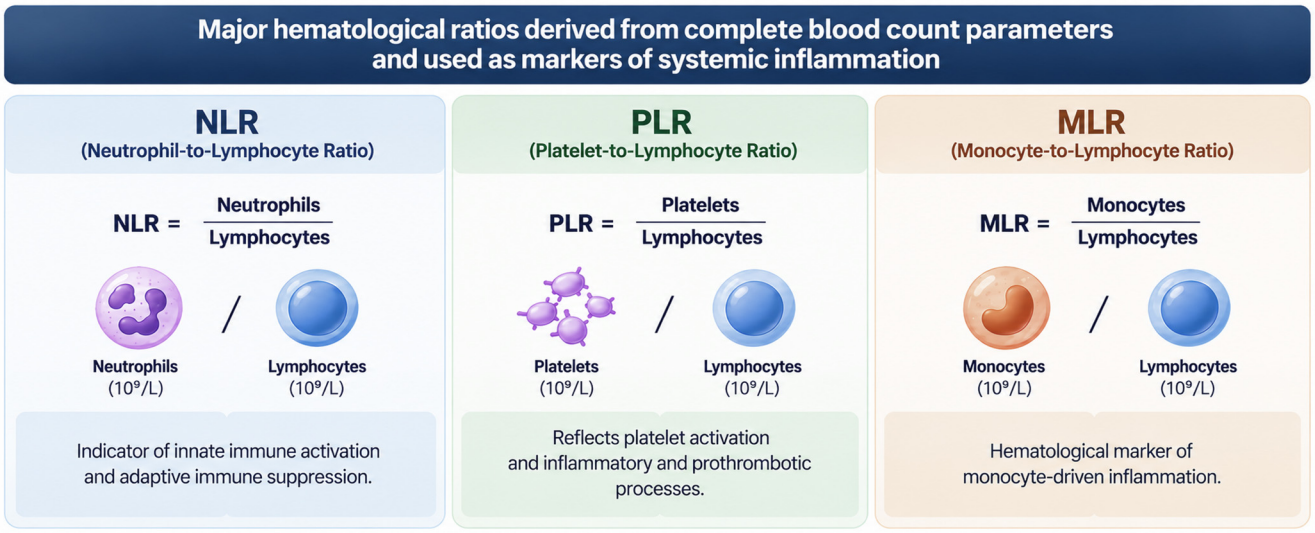

Figure 4. Major hematological ratios derived from complete blood count parameters and used as markers of systemic inflammation. The schema was generated with the assistance of Gemini Notebook. Legend: Neutrophil-to-lymphocyte ratio (NLR), Platelet-to-lymphocyte ratio (PLR), Monocyte-to-lymphocyte ratio (MLR).

The NLR is one of the most extensively investigated hematological ratios in the context of obesity and MetS. Derived from neutrophil and lymphocyte counts, it reflects the balance between cellular components of the innate and adaptive immune responses. In individuals with obesity, higher NLR values have been associated with insulin resistance, hs-CRP, TNF-α, visceral adiposity, and increased carotid intima–media thickness, suggesting a relationship with metabolic and cardiovascular abnormalities [48–50].

In the study by Surendar et al. [32], individuals with MetS exhibited significantly higher NLR values than those without the syndrome. Moreover, a progressive increase in NLR was observed with an increasing number of MetS components. Similar findings were reported by Sánchez-Autet et al. [51] in patients with bipolar disorder, in whom higher NLR values were associated with a higher Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index, a greater number of MetS risk factors, and a less favorable metabolic profile. In the same study, elevated hs-CRP levels were associated with abdominal obesity and greater waist circumference [32,51].

A meta-analysis including 70,937 individuals found that patients with MetS had significantly higher NLR values than healthy controls. The study also reported that elevated NLR was associated with more than a twofold higher risk of MetS, establishing an association between NLR and MetS [13]. The PLR, in turn, incorporates the contribution of platelets to inflammatory and atherothrombotic processes. Individuals with obesity may exhibit alterations in platelet counts and platelet-related indices; however, the association between

PLR and MetS appears to be less consistent than those observed for hs-CRP and NLR, with weaker and more variable relationships with anthropometric parameters and individual components of the syndrome [47,51].

The MLR has been investigated as a potential marker of systemic inflammation in metabolic disorders. However, evidence directly linking MLR to MetS remains inconclusive. A systematic review and meta-analysis found no statistically significant difference in MLR between individuals with and without MetS, with substantial heterogeneity across studies [52]. A recent cross-sectional study reported an increase in MLR with a greater number of MetS components; however, this association was not retained after multivariable adjustment. Therefore, the independent clinical value of MLR for identifying MetS remains uncertain [53].

Overall, the available evidence indicates that hs-CRP, leukocyte and neutrophil counts, and the NLR, PLR, and MLR may reflect different aspects of the systemic inflammatory response associated with obesity and MetS. Among these markers, NLR is supported by the most consistent body of evidence within the studies reviewed, particularly regarding its association with the presence and number of MetS components. In contrast, findings for PLR are less consistent, whereas MLR remains comparatively less well characterized in the specific context of MetS [13,47,54].

When interpreting this evidence, a distinction should be made between studies that enrolled participants specifically defined by MetS and studies that evaluated broader populations with obesity, T2DM, or CVD. The association between NLR and MetS is supported by MetS-specific samples [13,48]. In contrast, several reports on PLR, SII, SIRI, and PIV derive from obesity- or diabetes-based cohorts, in which these indices may primarily capture adiposity- or glycemia-related inflammation rather than the syndrome itself. This distinction is relevant because indices strongly associated with obesity or T2DM may show weaker or inconsistent associations when MetS is the outcome of interest [12,14].

5.2. Composite Inflammatory Indices

In addition to complete blood count-derived ratios, composite inflammatory indices, including the SII, SIRI, and PIV, have been investigated as potential biomarkers capable of integrating different components of the immune and inflammatory responses. SII is calculated as the product of platelet and neutrophil counts divided by the lymphocyte count, whereas SIRI is calculated as the product of neutrophil and monocyte counts divided by the lymphocyte count. PIV, in turn, integrates neutrophil, platelet, and monocyte counts relative to the lymphocyte count [55–58]. Collectively, these indices incorporate information related to innate and adaptive immunity as well as thrombo-inflammatory activity, thereby providing a more comprehensive assessment of systemic inflammatory status [12]. The cellular components and formulas used to calculate these indices are presented in Figure 5.

The SII was originally developed as a prognostic marker in patients with hepatocellular carcinoma [59] and has also shown prognostic value in other oncological settings [56]; it has subsequently been investigated in metabolic disorders because of its ability to capture inflammatory and thrombotic components involved in atherogenesis [57].

In an analysis based on data from the NHANES 2011–2016, including more than 12,000 adults, higher SII levels were significantly associated with the presence of MetS. After adjustment for multiple potential confounders, individuals in the highest SII quartile had an approximately 33% higher likelihood of MetS compared with those in the lowest quartile. Positive associations were also observed between SII, increased waist circumference, and hypertension [58].

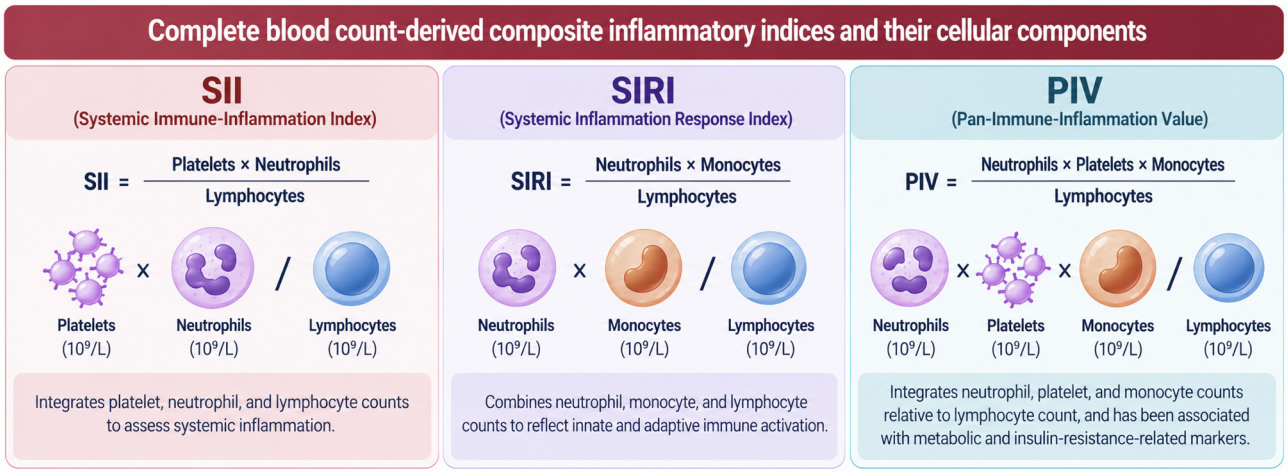

Figure 5. Complete blood count-derived composite inflammatory indices and their cellular components. The schematic was generated with the assistance of Gemini Notebook. Legend: Systemic immune-inflammation index (SII), Systemic inflammation response index (SIRI), Pan-immune-inflammation value (PIV).

Similar findings were reported in the MESA cohort, in which higher SII values were associated with a greater prevalence of MetS, hyperglycemia, and hypertension; individuals in the highest SII quartile exhibited a higher prevalence of these metabolic abnormalities compared with those with lower index values [15]. In an independent cross-sectional analysis of U.S. adults, higher SII was likewise associated with MetS and its components [60].

In an analysis of U.S. adults, higher SIRI values were associated with obesity [57], and in individuals with obesity, elevated SIRI predicted all-cause and cardiovascular mortality [14]. Moreover, data from NHANES have demonstrated an association between higher SIRI levels and more advanced stages of cardiovascular–kidney–metabolic syndrome, with individuals in the highest quartile exhibiting a greater likelihood of advanced CVD [61]. Associations of SIRI with CVD have also been reported in obese individuals [62].

Furthermore, in a prospective cohort of 85,154 individuals followed for 10 years, higher SII and SIRI values were associated with increased risks of stroke and all-cause mortality. Higher SIRI, but not SII, was also associated with MI in the overall analysis. These findings suggest potential prognostic relevance for selected cardiovascular outcomes; however, they do not establish the incremental predictive value of these indices beyond conventional risk assessment tools [63].

PIV is another emerging index derived from circulating immune cell counts and has been proposed as an integrative measure of systemic inflammation. In a study conducted by Ramasamy et al. involving 4620 participants from NHANES 2017–2020, higher PIVs were observed among individuals with obesity, diabetes, and MetS. Moreover, higher PIV quartiles were associated with increased values of the HOMA-IR, homeostatic model assessment of β-cell function (HOMA-B), lipid accumulation product (LAP), visceral adiposity index (VAI), and triglyceride–glucose index (TyG), suggesting a relationship between PIV and multiple surrogate markers of insulin resistance and metabolic risk [12].

Overall, SII, SIRI, and PIV integrate information from multiple circulating immune cell populations and have been associated with metabolic abnormalities, including MetS and its components [12,15,58,60]. However, these associations do not establish that composite indices provide additional clinical information beyond conventional hematological markers such as NLR. Although longitudinal studies have linked SII and SIRI to selected cardiovascular outcomes and mortality, their incremental predictive value beyond conventional cardiometabolic risk assessment tools has not been established [14,63].

PIV has also been associated with insulin resistance and other metabolic risk markers, including HOMA-IR, LAP, VAI, and TyG [12]. Similarly, although hs-CRP has been investigated in relation to MetS and its components [42–45], it remains unclear whether SII, SIRI, or PIV provides additional information beyond this established inflammatory marker. Differences in study populations, evaluated outcomes, and methodological approaches, as well as the predominance of cross-sectional evidence for some indices, should be considered when interpreting these findings. Further prospective and comparative studies may help clarify the potential incremental clinical value of these composite indices alongside NLR, hs-CRP, and conventional cardiometabolic risk factors. The main findings, study designs, and limitations of the evidence for the conventional and composite hematological inflammatory indices are summarized in Table 1.

5.3. Comparison with Metabolic and Biochemical Inflammatory Markers: The Uric Acid-to-HDL Cholesterol Ratio (UHR)

In addition to complete blood count-derived indices, ratios calculated from routine biochemical parameters have been proposed as markers of metabolic–inflammatory burden. Among them, the UHR, obtained by dividing serum uric acid by HDL-C, has emerged as a simple and inexpensive biomarker. Its biological rationale lies in the opposing metabolic effects of its two components: uric acid is associated with oxidative stress, endothelial dysfunction, inflammasome activation, and impaired insulin signaling, whereas HDL-C exerts anti-inflammatory, antioxidant, and antiatherogenic effects and participates in reverse cholesterol transport. UHR may therefore integrate pro-inflammatory and protective metabolic pathways into a single measurable index [64,65].

Consistent with this rationale, elevated UHR has been associated with the presence of MetS and reported as a strong predictor of MetS in patients with T2DM, including the prediction of incident MetS over follow-up [64–66]. UHR has also been linked to insulin resistance, correlating with HOMA-IR and independently associated with insulin resistance in patients with T2DM [67]; to MASLD, with a 5.7% increase in the odds of MASLD for each unit increment in UHR after multivariable adjustment [68]; to poor blood pressure control in hypertension [69]; and to diabetic complications, including CVD and chronic kidney disease [70]. Furthermore, higher UHR has been associated with all-cause and cardiovascular mortality in the general population and in patients with diabetes or prediabetes, indicating that this ratio captures not only metabolic abnormalities but also their prognostic inflammatory dimension [71,72].

Table 1. Comparative Evidence on Hematological Inflammatory Indices in Metabolic Syndrome and Bariatric Surgery.

Index and Formula	Populations and Study Designs	Main Findings	Limitations and Considerations
Neutrophil-to-lymphocyte ratio (NLR) = Neutrophils/Lymphocytes	Cross-sectional studies, systematic reviews and meta-analyses, longitudinal studies, and BS cohorts.	NLR has been associated with the presence of MetS in observational studies and meta-analyses [13,32]. Associations with insulin resistance, visceral adiposity, and other cardiometabolic outcomes have also been reported in populations with obesity [48–50]. Evidence regarding the severity of MetS is less consistent. A reduction in NLR three months after sleeve gastrectomy was reported in a prospective study [73].	Findings may vary across populations and cutoff values. The relationship between NLR changes and long-term metabolic outcomes after BS requires further investigation.
Platelet-to-lymphocyte ratio (PLR) = Platelets/Lymphocytes	Cross-sectional studies of obesity and MetS; perioperative and postoperative BS cohorts.	Associations with obesity and MetS have been inconsistent [47,51]. PLR increased during postoperative follow-up in a sleeve gastrectomy cohort [16] and during the first 24 h after surgery [74].	Postoperative changes may reflect the inflammatory response to surgical trauma. Their interpretation in relation to metabolic improvement depends on the timing of assessment and clinical context.
Monocyte-to-lymphocyte ratio (MLR) = Monocytes/Lymphocytes	Systematic review and meta-analysis comparing individuals with and without MetS.	A meta-analysis of 63 studies found no statistically significant difference in MLR between individuals with and without MetS ($p = 0.27$), with substantial heterogeneity ($I^2 = 100\%$) [52].	Results do not establish a consistent association between MLR and MetS. Further studies are needed to clarify its relationship with metabolic abnormalities and its potential clinical relevance.
Systemic immune-inflammation index (SII) = Platelets × Neutrophils/Lymphocytes	Cross-sectional population studies, longitudinal studies of cardiovascular outcomes, and BS follow-up studies.	Higher SII values have been associated with MetS, hyperglycemia, and hypertension [15,60]. In NHANES data, the highest versus lowest SII quartile was associated with greater odds of MetS (OR: 1.33; 95% CI: 1.14–1.55) [58]. SII has also been associated with stroke and all-cause mortality [63]. A decrease after BS was reported at three months [75].	Associations with MetS are primarily based on observational data. The contribution of SII to risk prediction beyond established clinical variables and the consistency of its changes over long-term postoperative follow-up remain to be clarified.

Table 1. *Cont.*

Index and Formula	Populations and Study Designs	Main Findings	Limitations and Considerations
Systemic inflammation response index (SIRI) = Neutrophils × Monocytes/Lymphocytes	Cross-sectional studies of obesity and metabolic outcomes, population-based mortality studies, and longitudinal cardiovascular cohorts.	Associated with obesity [57] and with all-cause and cardiovascular mortality in an obese population [14]. Associations with cardiovascular outcomes and mortality have also been reported in longitudinal cohorts [63].	Observational associations do not establish causality. Further research is needed to determine its clinical value, establish interpretable thresholds, and assess its performance in different populations, including patients undergoing BS.
Pan-immune-inflammation value (PIV) = Neutrophils × Platelets × Monocytes/Lymphocytes	Cross-sectional population-based studies and a prospective cohort of patients undergoing sleeve gastrectomy.	Associated with obesity, diabetes, MetS, and several insulin-resistance and adiposity-related indices [12]. In a prospective sleeve gastrectomy cohort, PIV increased during the first 24 h after surgery and showed potential for predicting early postoperative complications [74].	Metabolic associations are mainly derived from cross-sectional studies. The predictive findings reported in the perioperative setting require confirmation in independent populations, and long-term postoperative data remain scarce.

Abbreviations: BS, bariatric surgery; CI, confidence interval; MetS, metabolic syndrome; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; PIV, pan-immune-inflammation value; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

Compared with complete blood count-derived indices, UHR offers a complementary rather than competing profile. The NLR, PLR, MLR, SII, SIRI, and PIV capture the cellular arm of systemic inflammation, reflecting the balance between innate and adaptive immune cell populations and thrombo-inflammatory activity [14,48,49,57,58]. In contrast, UHR reflects the biochemical arm of the metabolic–inflammatory axis, combining a pro-oxidant, pro-inflammatory analyte with an anti-inflammatory lipoprotein that is directly involved in the atherogenic dyslipidemia that characterizes MetS [64,65]. From a practical standpoint, both families of markers share relevant advantages, including low cost, derivation from routinely performed laboratory panels, and ease of calculation [65,76].

However, neither UHR nor complete blood count-derived indices should be regarded as standalone diagnostic tools. The discriminatory performance reported for UHR has been modest, with areas under the receiver operating characteristic curve (AUC) of 0.624 for prediabetes and 0.665–0.717 for insulin resistance [67,76]. These findings should be interpreted in relation to the specific outcomes and populations investigated. They cannot be directly compared with the associations reported for NLR and SII, as these findings involve different statistical measures and do not necessarily assess the same diagnostic or predictive outcomes. Furthermore, standardized cutoff values remain lacking across these biomarker families. Direct head-to-head studies comparing UHR with complete blood count-derived inflammatory indices in individuals with MetS are currently unavailable [65,66,77,78]. Further research is warranted to determine whether their combined use, capturing complementary cellular and biochemical aspects of the metabolic–inflammatory axis, provides incremental value for cardiometabolic risk stratification.

5.4. Hematological Inflammatory Indices in the Context of Bariatric Surgery

BS is an established therapeutic intervention for severe obesity and can promote sustained weight loss and improvements in metabolic abnormalities. In this context, the reduction in visceral adiposity following procedures such as sleeve gastrectomy is associated with decreased secretion of pro-inflammatory cytokines, reduced recruitment of inflammatory cells into adipose tissue, and improved insulin sensitivity. These changes are accompanied by alterations in circulating inflammatory markers during the postoperative period. When interpreting hematological indices after BS, two distinct time windows must be considered: the acute perioperative phase, which reflects the inflammatory response to surgical tissue injury, and the medium- to long-term postoperative phase, which may reflect weight loss and improvement in metabolic–inflammatory status [17–20,77–86].

In the immediate postoperative period, hematological indices primarily capture the systemic inflammatory response to surgical trauma rather than metabolic improvement. In a prospective controlled study, Kutluer et al. evaluated PLR, NLR, and PIV before and 24 h after laparoscopic sleeve gastrectomy. Preoperatively, differences in leukocyte and neutrophil counts and PIVs were observed between patients with and without postoperative complications. When preoperative and postoperative values were compared, NLR, PLR, and PIV all increased significantly within 24 h, consistent with an acute-phase response to surgical tissue injury. According to the authors, PIV demonstrated greater sensitivity and specificity than NLR and PLR for predicting early major surgical complications following laparoscopic sleeve gastrectomy, although these preliminary findings from a single prospective cohort require external validation before any perioperative application. These acute-phase findings should therefore not be interpreted as measures of metabolic inflammation, and they underscore that the prognostic meaning of an index is time-dependent after surgery [74].

Beyond the acute phase, sustained weight loss and metabolic improvement may modulate systemic inflammatory activity. In patients who underwent sleeve gastrectomy, a significant reduction in NLR was observed over a one-year follow-up period, accompanied by reductions in BMI, improvements in metabolic and hepatic parameters, and substantial regression of hepatic steatosis. However, no direct correlation was identified between the magnitude of NLR reduction and the improvement in hepatic steatosis assessed by ultrasonography, although weight loss was associated with a reduction in systemic inflammation [87].

In a retrospective analysis, elevated preoperative NLR values were associated with early postoperative complications following BS, with a cutoff of 2.67 identified as associated with a higher likelihood of surgical complications. This threshold is specific to the study population and should not be generalized to other clinical settings without external validation. Although these findings suggest a potential association between preoperative inflammatory status and postoperative outcomes, prospective studies are needed to establish the reproducibility, predictive performance, and clinical applicability of this cutoff [88].

Metabolic improvements following BS have also been associated with changes in NLR. Some studies have reported positive correlations between preoperative NLR and insulin levels, insulin resistance, and fasting blood glucose. Patients with lower preoperative NLR values exhibited more favorable weight-loss outcomes and higher rates of T2DM remission during follow-up, suggesting that the degree of preoperative systemic inflammation may be associated with the metabolic response to surgical treatment [89].

The PLR has also been evaluated following BS, as it may reflect both inflammatory processes and thrombotic activity. Although some studies have not identified consistent associations between PLR and preoperative metabolic parameters, changes in this index have been observed alongside clinical improvements after surgery. In patients undergoing

sleeve gastrectomy, an increase in PLR was reported during follow-up and was associated with reductions in BMI and improvements in some obesity-related comorbidities. The direction and determinants of long-term PLR changes therefore appear inconsistent across studies [16].

Composite inflammatory indices, including SII, SIRI, and PIV, may also have potential for monitoring obesity- and MetS-related inflammatory changes. Studies have reported associations between these indices and obesity, MetS, T2DM, CVD, and cardiometabolic risk factors [12,14,15]. However, studies specifically evaluating these indices as markers of medium- or long-term response to BS remain limited. Among the available evidence, a recent study reported a reduction in SII following metabolic and BS, whereas evidence specifically addressing postoperative changes in SIRI and PIV beyond the acute phase remains more limited [75].

Importantly, even long-term changes in hematological indices after BS should be interpreted with caution. Postoperative modifications in nutritional status, micronutrient deficiencies, and shifts in leukocyte subpopulations may independently influence neutrophil, lymphocyte, and monocyte counts. Whether sustained longitudinal changes in these indices specifically reflect resolution of metaflammation, rather than these concurrent factors, remains to be established in studies with standardized postoperative assessment time points [18–20,73].

Overall, postoperative changes in hematological inflammatory indices should be interpreted according to the time elapsed since BS. During the first hours to days, increases in NLR, PLR, and PIV primarily reflect the acute inflammatory response to surgical tissue injury rather than worsening metabolic inflammation. In contrast, changes over subsequent months may accompany sustained weight loss and metabolic improvement, although patterns vary across indices. Long-term reductions in NLR have been reported, whereas findings for PLR and composite indices remain less consistent. These changes may also be influenced by nutritional status, micronutrient availability, and shifts in leukocyte populations. Prospective studies with standardized assessment time points are needed to clarify these trajectories and establish their clinical and prognostic value [73–75,88].

6. Clinical Applicability of Inflammatory Indices and Therapeutic Perspectives

6.1. Hematological Inflammatory Indices in the Monitoring of Metabolic Syndrome

Chronic low-grade systemic inflammation represents one of the key mechanisms involved in the pathophysiology of MetS and is closely associated with visceral obesity, insulin resistance, oxidative stress, immune dysfunction, and alterations in the gut microbiota. In this context, monitoring inflammatory biomarkers may contribute to a better understanding of metabolic changes over time and facilitate the assessment of MetS-related abnormalities [6,7].

Conventional inflammatory biomarkers, such as hs-CRP, TNF-α, and IL-6, may have limitations related to cost and widespread availability. In contrast, complete blood count-derived inflammatory indices, including the NLR, PLR, MLR, SII, SIRI, and PIV, can be readily calculated from routine laboratory tests. This characteristic may facilitate their use across different clinical settings, particularly when an accessible assessment of systemic inflammatory status is required [10,47].

Reduction in visceral adiposity through lifestyle interventions has been associated with decreased production of pro-inflammatory cytokines, improved insulin sensitivity, and lower hs-CRP levels. Accordingly, weight loss and lifestyle modification may influence inflammatory biomarkers used to monitor individuals with MetS [35,90,91].

The therapeutic management of obesity and MetS remains primarily based on intensive lifestyle modification, including caloric restriction, dietary modification, and increased physical activity. Weight loss corresponding to 5–10% of initial body weight has been associated with clinically meaningful improvements in glycemic control, blood pressure, and inflammatory biomarkers [92]. Regular physical activity also exerts anti-inflammatory effects, and interventions combining exercise with caloric restriction may reduce inflammatory markers in adults with overweight or obesity [91,93].

An additional aspect reported in the literature is the potential influence of physical activity on the relationship between inflammation and adiposity. In a study involving 7645 adults, increasing SII levels were observed alongside higher anthropometric indicators of adiposity, whereas regular physical activity appeared to partially attenuate this association, suggesting a potential modulatory effect of exercise on obesity-related systemic inflammation [94]. In this context, serial assessment of hematological inflammatory indices has been proposed as a research approach to track inflammatory changes. However, their value for therapeutic monitoring remains unproven and requires validation against established markers, despite their widespread availability and low cost [26,40,86,89].

6.2. Pharmacological Strategies and Inflammatory Modulation

When lifestyle interventions alone do not achieve adequate therapeutic outcomes, anti-obesity pharmacotherapy may be considered. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as semaglutide, and dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonists, such as tirzepatide, can induce substantial reductions in body weight, improve insulin resistance, and provide cardiovascular benefits. These agents exert their effects primarily by enhancing satiety, delaying gastric emptying, and reducing energy intake [92,95].

In addition to medications specifically used for obesity treatment, several pharmacological therapies employed in the management of MetS may exert additional anti-inflammatory effects. These include metformin, GLP-1 RAs, sodium–glucose cotransporter 2 (SGLT2) inhibitors, statins, and thiazolidinediones. In addition to controlling specific cardiometabolic risk factors, these therapies have been associated with reductions in systemic inflammatory activity and, for several drug classes, a lower incidence of cardiovascular events [35,92].

Reduction in visceral adiposity represents an important mechanism underlying the metabolic and inflammatory effects of these interventions, as a decrease in dysfunctional adipose tissue is associated with reduced production of pro-inflammatory cytokines, improved insulin sensitivity, and lower hs-CRP levels [35,38]. In this context, no study to date has validated these indices as markers of treatment response; this application therefore remains hypothetical and requires further clinical validation [13,88].

Beyond currently available pharmacological therapies, strategies specifically targeting the inflammatory mechanisms underlying MetS are being investigated, including interventions targeting inflammasome activation, inflammatory cytokine signaling, and modulation of the gut microbiota. These approaches represent potential future therapeutic strategies, given the central role of chronic low-grade inflammation in the pathophysiology of MetS [6,7].

Despite the expanding range of pharmacological options, sustained lifestyle modification remains a cornerstone of MetS management. However, long-term adherence to lifestyle interventions and achievement of clinically meaningful weight loss may be challenging, highlighting the need to investigate complementary therapeutic approaches targeting dysfunctional adipose tissue accumulation and the associated chronic low-grade systemic inflammatory state. In this context, modulation of inflammasome activation and the com-

plement system has been proposed as a potential therapeutic avenue warranting further investigation [10].

6.3. Clinical Applicability and Limitations of Hematological Inflammatory Indices

Complete blood count-derived hematological inflammatory indices have several characteristics that support their investigation as complementary tools for assessing systemic inflammation associated with MetS. Their derivation from routine laboratory tests, low cost, and widespread availability represent important advantages for their potential application across different clinical settings. However, these indices should be interpreted as complementary biomarkers rather than substitutes for the clinical, metabolic, and conventional inflammatory parameters routinely used in the assessment of MetS [12,13,47,57,60].

The potential clinical value of hematological inflammatory indices should be considered alongside established metabolic determinants of obesity-related complications. In a study of patients undergoing BS, insulin resistance was independently associated with NASH, whereas HbA1c and insulin resistance independently predicted hepatic steatosis. These findings highlight the relevance of metabolic factors when assessing obesity-related complications and suggest that hematological inflammatory indices should be interpreted as potentially complementary markers rather than substitutes for established metabolic parameters [96].

An additional limitation inherent to these indices is their limited specificity as markers of systemic inflammation. Because NLR, PLR, MLR, SII, SIRI, and PIV are calculated from circulating blood cell counts, their values may be influenced by conditions unrelated to metabolic inflammation, including acute or chronic infections, autoimmune and other inflammatory diseases, hematological disorders, malignancy, and chronic kidney or liver disease [97,98]. Smoking, alcohol consumption, age, sex, race/ethnicity, physical activity, and circadian variation may also affect hematological parameters and, consequently, the derived indices [98,99]. Medications that alter leukocyte counts, including corticosteroids, chemotherapy, and granulocyte colony-stimulating factors, represent additional potential confounders [97,100]. Recent surgery constitutes an additional relevant confounder, as transient postoperative increases in these indices reflect the acute inflammatory response to surgical tissue injury rather than metabolic inflammation [74].

None of the studies reviewed applied standardized protocols to exclude or adjust for all these factors, and their potential confounding effects on the associations observed in MetS remain insufficiently quantified. Consequently, an isolated elevation in any of these indices cannot be attributed specifically to metabolic inflammation without appropriate clinical assessment, and population-level associations should not be directly extrapolated to individual-level interpretation [98,99,101].

The heterogeneity of the available evidence represents one of the major limitations to the incorporation of these biomarkers into routine clinical practice. Differences in the characteristics of the populations studied, diagnostic criteria used to define MetS, evaluated outcomes, and methods used to categorize or analyze these indices hinder direct comparisons across studies and the establishment of reference values applicable to different populations. Furthermore, although associations between hematological inflammatory indices and various components of cardiometabolic risk have been reported, their predictive performance has not yet been sufficiently established to support their use as standalone tools for risk stratification [87,88].

In the context of BS, postoperative changes in hematological inflammatory indices suggest that these biomarkers may reflect changes associated with weight loss and the systemic inflammatory response. However, available studies differ in terms of surgical procedures,

follow-up duration, assessment time points, and evaluated outcomes, limiting conclusions regarding their utility for postoperative monitoring and prognostic assessment [73,74,87,88].

Therefore, the clinical use of hematological inflammatory indices should be considered within a broader framework integrating clinical and laboratory information. Further prospective studies involving well-characterized populations and standardized assessment protocols are needed to establish clinically meaningful cutoff values, determine their predictive performance, and identify the specific settings in which these biomarkers may provide incremental information for cardiometabolic risk assessment [87,88]. Furthermore, given the non-specificity of these indices, any future application will require predefined criteria for excluding or adjusting for concomitant conditions that affect blood cell counts, as well as demonstration that index-guided decisions add value over established clinical and laboratory assessment [98,100].

7. Conclusions

Hematological inflammatory indices derived from the complete blood count and biochemical ratios such as UHR have been associated with MetS and cardiometabolic abnormalities, although the strength and consistency of the evidence vary across indices and study populations. NLR is among the most extensively investigated indices in MetS-specific populations, whereas evidence for PLR, MLR, SII, SIRI, and PIV remains limited or inconsistent. Findings from populations with obesity, type 2 diabetes, or CVD should not be directly extrapolated to MetS. Moreover, the lack of specificity of these indices and their susceptibility to clinical confounders limit their interpretation as markers of metabolic inflammation.

Following BS, changes may reflect both metabolic improvements and postoperative factors, including surgical stress, nutritional changes, and alterations in blood cell counts, while their long-term clinical significance remains uncertain. The lack of validated cutoffs, standardized assessment protocols, and demonstrated incremental predictive value beyond established clinical markers precludes their routine clinical implementation. Further prospective studies are needed to clarify their reproducibility, prognostic value, and potential to provide additional information beyond established clinical and laboratory markers.

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Abbreviations

The following abbreviations are used in this manuscript:

AUC	Area under the curve
BMI	Body mass index
BS	Bariatric surgery
CD8+	Cluster of differentiation 8-positive
CVD	Cardiovascular disease
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1 RAs	Glucagon-like peptide-1 receptor agonists
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
hs-CRP	High-sensitivity C-reactive protein
IL-6	Interleukin-6
LAP	Lipid accumulation product
M1	Pro-inflammatory macrophages
M2	Anti-inflammatory macrophages
MASLD	Metabolic dysfunction-associated steatotic liver disease
MASH	Metabolic dysfunction-associated steatohepatitis
MCP-1	Monocyte chemoattractant protein-1
MetS	Metabolic syndrome
MI	Myocardial infarction
MLR	Monocyte-to-lymphocyte ratio
NF-κB	Nuclear factor kappa B
NLR	Neutrophil-to-lymphocyte ratio
PIV	Pan-immune-inflammation value
PLR	Platelet-to-lymphocyte ratio
SGLT2	Sodium–glucose cotransporter 2
SII	Systemic immune-inflammation index
SIRI	Systemic inflammation response index
T2DM	Type 2 diabetes mellitus
TNF-α	Tumor necrosis factor-alpha
TyG	Triglyceride–glucose index
UHR	Uric acid-to-HDL cholesterol ratio
VAI	Visceral adiposity index

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