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Unraveling the clinical significance and prognostic value of the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, systemic inflammation response index, and delta neutrophil index: An extensive literature review

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Abstract:

In the field of critical care medicine, substantial research efforts have focused on identifying high-risk patient groups. This research has led to the development of diverse diagnostic tools, ranging from basic biomarkers to complex indexes and predictive algorithms that integrate multiple methods. Given the ever-evolving landscape of medicine, driven by rapid advancements, changing treatment strategies, and emerging diseases, the development and validation of diagnostic tools remains an ongoing and dynamic process. Specific changes in complete blood count components, such as neutrophils, lymphocytes, monocytes, and platelets, are key immune system responses influenced by various factors and crucial in systemic inflammation, injury, and stress. It has been reported that indices such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and delta neutrophil index calculated using various ratios of these elements, are important predictors of various outcomes in conditions where the inflammatory process is at the forefront. In this narrative review, we concluded that NLR, PLR, SII, and SIRI show promise in predicting outcomes for different health conditions related to inflammation. While these tests are accessible, reliable, and cost-effective, their standalone predictive performance for a specific condition is limited.

Keywords:

Delta neutrophil index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune inflammation index, systemic inflammation response index

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Introduction

Within the medical literature, identifying high-risk patient groups within critically ill populations, such as cancer, sepsis, polytrauma, acute ischemic stroke, and acute coronary syndrome, has been a

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notable research emphasis. To fulfill this goal, a variety of diagnostic tools have been developed over time. These tools vary in complexity, ranging from straightforward biomarkers based on single measurements to more intricate indexes that consider ratios, as well as sophisticated prediction models and algorithms that integrate multiple methods.

The literature regarding diagnostic accuracy is well-rounded and exhibits a dynamic nature. Due to rapid developments in the field of medicine, changes in treatment approaches, and the growing significance of newly emerging diseases or conditions, the process of developing new diagnostic tools or validating the existing ones remains ongoing.

The concept of the neutrophil-to-lymphocyte ratio (NLR), initially proposed by Zahorec in 2001, stands as a noteworthy outcome of these efforts.[1] Just like the shock index, this new parameter, which is formulated by the ratio of two simple complete blood count parameters, has been found to provide better results in the prognosis of many critical conditions than its components, thus laying the foundation of a fairly extensive literature.

In this comprehensive narrative review, our objective was to cover the literature on four widely studied parameters-NLR, platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and delta neutrophil index (DNI) while highlighting pivotal points and significant insights.

Neutrophil-to-lymphocyte Ratio

Neutrophilia and lymphocytopenia, which are immune system responses to systemic inflammation, injury, and stress, are influenced by various factors.[2] Neutrophils serve as precursors to the innate immune response, engaging in phagocytosis and releasing cytokines and mediators.[3] They act as the main effectors in the early hyperdynamic phase of infection and contribute to adaptive immunity regulation.[4] Conditions such as infection, acute stroke, myocardial infarction, atherosclerosis, severe trauma, burns, major surgery, and any situation involving tissue damage activating SIRS can lead to increased neutrophil counts.[5]

Neutrophilia during systemic inflammation occurs due to neutrophil demargination, suppressed neutrophil apoptosis, and stem cell stimulation through growth factors such as G-CSF.[6,7] Endocrine stress responses marked by elevated serum cortisol and catecholamines, or triggered by sympathetic activation, can also raise neutrophil count.[8,9]

Lymphocytopenia, a notable decrease in circulating lymphocyte count, is described after malignity, severe trauma, major surgery, severe sepsis, and systemic inflammation.[2,8,10] This decrease in lymphocytes, indicative of depressed cell-mediated immunity, has been extensively studied. For instance, in cases such as multiple trauma and major surgery, neuroendocrine stress and tissue injury alter the T4/T8 lymphocyte ratio, causing lymphocytopenia within 6 h, lasting 2–7 days.[8,11] The mechanisms responsible for lymphopenia also involve margination and redistribution of lymphocytes within the lymphatic system, along with increased apoptosis through tumor-related cytokines (particularly interleukin [IL-10] and tumor necrosis factor beta).[6,12] Moreover, factors such as ischemia-reperfusion injury (e.g., myocardial infarction) and upregulated pro-inflammatory cytokines (e.g., acute pancreatitis) contribute to lymphocytopenia.

Simultaneous yet opposite changes in neutrophil and lymphocyte counts reflect a multifactorial dynamic response, influenced by immunologic, neuroendocrine, humoral, and biological factors, adding a layer of complexity and interest to this phenomenon.[6] In addition, the early change (<6 h) in neutrophil and lymphocyte counts following acute physiological stress endows them as earlier markers compared to other laboratory parameters (e.g., white blood cell count and C-reactive protein [CRP]).

Although the separate role of neutrophil and lymphocyte counts in the clinical severity of systemic inflammatory response has been previously examined, the neutrophil-lymphocyte ratio (NLR) was identified by Zahorec in 2001.[1,10,11] NLR, the ratio of neutrophil and lymphocyte counts (in absolute and/or relative % values), has been proposed as a simple, reliable, and cost-effective severity parameter of various stressful events (peritonitis, abdominal sepsis, complicated postsurgical period, severe sepsis, and septic shock) in critically ill patients. In subsequent research, it has been reported that the NLR is more reliable in predicting patient survival compared to neutrophil or lymphocyte counts alone.[11,13]

When examining the reported normal values of NLR in healthy adults of diverse races worldwide, the median NLR appears to be 1.65 (range 1.2–2.15).[9] While NLR values below 5 are considered normal in the original study, distinct cutoff values have been reported for different diseases (e.g., malignity, sepsis, and cardiovascular diseases), and there remains a lack of consensus on a unified pathological value in this regard.

Recognizing the link between cancer-related systemic inflammation and elevated NLR levels, numerous studies

have explored the prognostic value of NLR in various solid tumors, especially in gastrointestinal malignancy.[14-23] In a large-scale analysis of 40,559 patients, Templeton *et al*. demonstrated that an NLR greater than 4 independently predicts diminished overall survival in multiple tumors (hazard ratio [HR] =1.81; 95% confidence interval [CI] =1.67–1.97).[24] However, the majority of meta-analyses identify an NLR cutoff value above 3.0 (interquartile range = 2.5–5.0) as a credible index for assessing the prognosis of a variety of solid tumors including colorectal, gastric, esophageal, pancreatic, liver, urological, and gynecological cancers.[9,19-21] NLR not only holds independent prognostic relevance for overall, cancer-free, and cancer-specific survival, but also proves valuable in monitoring various oncological therapies, and stratification of cancer as it correlates with tumor size, tumor stage, metastatic potential, and lymphatic invasion.[21,22,25-28]

NLR has been well recognized as a convenient marker for the diagnosis of bacteremia and sepsis. Its sensitivity in the diagnosis of bacteremia, infection, and sepsis has been validated in numerous studies.[29-32] A recent meta-analysis of 11,564 patients with sepsis indicated that a higher NLR was independently associated with poor clinical prognosis in patients with sepsis (mean HR = 1.75; 95% CI = 1.56–1.97). NLR was significantly higher in nonsurvivors than in survivors (mean HR = 1.18; 95% CI = 0.42–1.94).[33] The majority of the existing studies indicate that NLR ≥5 serves as a valid indicator of sepsis, while values above 10 are considered significant in septic shock.[34,35] It has also been suggested that not only high NLR values but also lower-than-expected NLR values (0.1–0.7) are associated with 28-day mortality.[36] While it has been suggested that NLR is more accurate and cost-effective than CRP as a marker of sepsis, its superiority over procalcitonin has not been established.[31,34,37] NLR also has good diagnostic accuracy in neonatal sepsis (area under the curve [AUC] = 0.87; 95% CI = 0.84–0.89).[38]

The relationship between NLR and pneumonia/respiratory failure has been extensively researched in the literature. NLR has shown a strong predictive utility in terms of short- and long-term mortality, ICU admission, and rehospitalization in community-acquired pneumonia.[39-41] Furthermore, NLR stands as the most extensively investigated biomarker in COVID-19 pneumonia due to the remarkable impact of SARS-CoV-2 infection on the immune system and its complex effects.[42] NLR is an independent prognostic marker for stratifying disease severity and mortality in patients with COVID-19. The majority of the existing systematic reviews or meta-analyses show a higher NLR ratio (≥5–7) on admission predicts both severity and mortality in COVID-19 patients.[8,43,44] According to a recent comprehensive analysis, using an NLR cutoff value of ≥6.5 accurately predicted mortality with a high rate (AUC = 0.90; 95% CI 0.87–0.92), and using a cutoff of ≥4.5 was effective in determining the severity of the disease (AUC = 0.85; 95% CI 0.81–0.88).[45] Beyond initial NLR, dynamic changes during hospitalization matter as increasing NLR during the clinical course links to severity and poor outcomes in COVID-19.[46,47] There was a 10% increase in the risk of in-hospital mortality per unit increase in NLR (OR = 1.10; 95% CI = 1.05–1.14).[44] Considering these findings, it is clear that NLR holds better diagnostic value than other hematological indices and biochemical markers, in the case of COVID-19. However, it remains evident that NLR alone cannot replace comprehensive scoring systems in clinical assessment.

NLR's predictive role in cardiovascular events is supported by various studies. Shah *et al*. established NLR >4.5 as an independent predictor of long-term coronary heart disease mortality in healthy populations.[48] A large meta-analysis involving over 16,000 patients determined that high NLR on admission was associated with higher overall mortality both in patients with STEMI and NSTEMI (OR = 4.60; 95% CI: 2.84–7.45, and OR = 6.41; 95% CI: 2.65–15.50, respectively) compared to low NLR. A higher MACE risk was observed in STEMI patients with high initial NLR (OR = 3.71; 95% CI: 2.67–5.17).[49] Recently, NLR also was found to be an independent predictor of short- and long-term adverse outcomes in acute heart failure.[50] In conclusion, evidence highlights the promising role of NLR in enhancing diagnosis and prognosis prediction in various cardiac pathologies, particularly when combined with cardiac markers and scoring systems.

The association between high NLR and increased risk of venous thromboembolism (VTE) in patients with malignancy has been recognized (HR = 1.2; 95% CI = 1.0–1.4), and it has recently been shown that NLR is associated with an increased risk of VTE (including pulmonary embolism [PE], deep vein thrombosis (DVT), and cerebral venous thrombosis (CVT) in non-cancer patients and can predict recurrence but may not be sufficient to distinguish the subtypes.[51,52] A meta-analysis of 2023 also revealed that NLR has a moderate prognostic value in the diagnosis of DVT in non-cancer patients (AUC = 0.74; 95% CI = 0.70–0.78), even though the cutoff values vary across the different studies.[53]

Among the subjects studied it was found that in patients with diabetes mellitus, NLR independently predicted major adverse cardiac events (MACEs).[54] Notably, NLR showed a significant increase in cases

of gestational diabetes.[55] Furthermore, in patients with type 2 diabetes mellitus, NLR independently predicted poor glycemic control (OR: 1.809; 95% CI = 1.459–2.401).[56]

Considering these findings, NLR serves as an accessible, cost-effective, and strong prognostic marker, for disease stratification and severity assessment in various stressful events, especially malignity, sepsis, and COVID-19 forefront. While definitive threshold values are lacking, NLR, when combined with reliable infection/inflammation biomarkers, plays a pivotal role in guiding decision-making and disease management. Future research can further clarify its optimal ranges and enhance its diagnostic utility.

Platelet-to-lymphocyte Ratio

Both thrombocytosis and lymphocytopenia are linked to the extent of systemic inflammation, while the ratio of the platelet to lymphocyte count introduces a fresh marker that integrates both hematologic parameters. Especially in conditions that are potent triggers of systemic inflammatory response such as sepsis, malignancy, rheumatologic disorders, and trauma, in addition to the previously mentioned neutrophilia and lymphopenia, platelet proliferation is induced by pro-inflammatory cytokines (particularly IL-6 and IL-1).[57,58] Thrombocytosis is linked to heightened inflammatory responses due to alterations in the body's microcirculation, augmented blood vessel permeability, platelet activation, and aggregation of a substantial number of platelets. Consequently, this exacerbates the overall inflammatory reaction within the body.

Platelets interact with tumor cells directly and contribute to tumor growth, invasion, and angiogenesis.[59] High platelet counts are associated with poor prognosis in colorectal, gastric, esophageal, and pancreatic cancers.[60,61] However, as an index, PLR was initially defined by Smith *et al*. in 2008.[62] While individual preoperative CA19-9 and PLR (cut-off value: 150) had low specificities (72% and 73%, respectively) for periampullary pancreatic tumor resectability, their combined model increased specificity to 96%. Furthermore, another study conducted by Smith *et al*. identified high PLR as an independent prognostic factor in pancreatic cancer, suggesting that PLR might serve as a superior prognostic marker compared to individual parameters or the NLR.[63]

However, the abundance of controversial data that does not support the original study is also noteworthy.[64-66] In a large-scale study with 27,031 cancer patients, high PLR value was revealed as a predictor of decreased overall survival, regardless of age, gender, and tumor site (AUC = 0.632; 95% CI = 0.620–0.644). However, it was not deemed superior to other systemic inflammation-based prognostic scores.[67] In a similar meta-analysis, it is concluded that a high PLR is independently associated with poorer overall survival across various solid tumors, and it is also not superior to other hematological indices (e.g., NLR, GPS).[68] In fact, subsequent studies indicated that even in pancreatic cancer, where PLR originally emerged, NLR demonstrated better performance in predicting prognosis.[69]

A large meta-analysis to investigate the prognostic role of PLR in various cancers indicated that elevated PLR significantly predicted poor overall survival (HR = 1.60; 95% CI = 1.35–1.90).[70] The relevant literature from the past 6 years suggests that the mean AUC value for PLR in predicting poor outcome in colorectal cancer was 0.648, with a cutoff of 146.98, alongside sensitivity of 67.83% and specificity of 60.65%, while NLR shows better diagnostic accuracy (AUC = 0.74 with a cutoff = 3.31, sensitivity = 63.03%, and specificity = 62.55%).[71] In conclusion, PLR is independently related to prognosis in many cancers, such as colorectal cancer, breast cancer, gastric cancer hepatocellular carcinoma, NSCLC, and SCLC.[72-77] Although the relationship between PLR and malignancy has been mostly investigated in the literature, the unpartially elucidated mechanism, varying diagnostic accuracy across ethnicities, and uncertainty in the cutoff values raise questions about the diagnostic utility of PLR in terms of malignancy.

Atherosclerosis, the primary cause of coronary artery disease (CAD), arises from an immune-inflammatory response. Activated platelets initiate thrombus formation on the rupture of atherosclerotic plaques or endothelial cell erosion, fostering atherothrombotic disease.[78] Consequently, platelet activation assumes a pivotal role in CAD and ACS.[79] Therefore, the predictive role of PLR in cardiovascular events is supported by various studies. In a recent analysis comprising a total of 6,627 acute coronary syndrome patients, it was revealed that an elevated PLR (>150) leads to a twofold increase in the risk of in-hospital all-cause mortality and cardiovascular mortality (pooled RR = 2.15; 95% CI = 1.73–2.67 and RR = 1.95; 95% CI = 1.30–2.91, respectively), as supported by similar studies.[80,81] In addition, studies have indicated a correlation between PLR and increased overall mortality in patients with NSTEMI.[82] Furthermore, a study demonstrated that elevated PLR is associated with the recurrence of myocardial infarction, stroke, and subsequent heart failure.[83] Considering these findings, an elevated PLR indicates the presence of inflammation, atherosclerosis, and coronary artery disease, and also serves as a prognostic indicator in cases of ACS.

Given the ease of calculating PLR and its widespread accessibility, further investigation is necessary to ascertain its diagnostic utility.

Multiple studies have demonstrated that elevated PLR values are associated with the presence and severity of rheumatologic diseases, particularly RA, SLE, and AS.[84] While the majority suggested the combination of PLR with NLR as a potentially valuable approach for the precise assessment of inflammatory activity in rheumatologic diseases.[80,85] Monitoring PLR and hematological indices hold the potential to aid in the follow-up of long-term anti-inflammatory and immunosuppressive therapies for rheumatic diseases. PLR also has been reported to predict the prognosis of sepsis, COVID-19, acute exacerbation of COPD, and PE.[86-90] However, its prognostic significance was not as successful as compared to NLR.

In conclusion, PLR is closely associated with systemic inflammation and is a promising biomarker not only in rheumatologic diseases but also in ACS, COVID-19, and various respiratory diseases. However, the challenges associated with determining the optimal cutoff range, coupled with the predominantly retrospective design of many studies, present significant concerns. More longitudinal studies are warranted to establish its diagnostic performance, alone or in combination with other parameters, in clinical practice.

Systemic Immune-inflammation Index

Another widely mentioned biomarker in the current literature is the SII which was initially defined by Hu *et al*. in 2014 and is calculated through the following formula: "*SII = Platelet x Neutrophil/Lymphocyte*".[91] The notion of the potential utility of this index is rooted in the special relationship between these cells, where neutrophils, lymphocytes, and platelets play pivotal roles in numerous inflammatory processes. It was originally developed for prognostication of patients with hepatocellular carcinoma after curative resection. Even though it exhibited poor predictive performance in overall survival (AUC = 0.680, 95% CI = 0.59–0.77), SII elicited a significant impact in the academic literature.

The systemic immune inflammation index has predominantly revolved around the examination of outcomes related to malignancy. In addition, a multitude of meta-analyses exploring prognostications for numerous cancer subtypes can be found in the existing literature. Researchers have examined specific groups of different types of cancers in various meta-analyses, revealing that SII emerged as a useful marker for overall survival, progression-free survival, and responsiveness to immunotherapy among cancer patients in general. A 2022 meta-analysis by Tian *et al*. comprising 14 articles and 2721 patients found that elevated SII levels (>750) indicate poor overall survival and progression-free survival (HR = 2.40; 95% CI = 2.04–2.82 and HR = 1.57; 95% CI = 1.33–1.86, respectively) in cancer patients who are medicated with immune checkpoint inhibitors.[92] Another meta-analysis consisting of 15 studies and 2438 patients examined the prognosis and responsiveness of cancer patients to immunotherapy and indicated that higher SII levels are associated with poor overall survival, objective response rate, and progression-free survival (HR = 2.33; 95% CI = 2.02–2.69, HR = 0.73; 95%CI = 0.56–0.94, and HR = 0.56; 95% CI = 0.35–0.88, respectively).[93]

Several meta-analyses examining the predictive value of SII report similar results in gynecological cancers, breast cancers, ovarian cancer, prostate cancer, renal cell carcinoma, small-cell lung cancer, gastric cancer, biliary tract cancer, pancreatic carcinoma, and nasopharyngeal carcinoma with an HR of overall survival ranging between 1.32 and 2.71.[93-102] Conversely, SII was not found to be a significant predictor of progression-free survival in small-cell lung cancer, gastric cancer, and renal cell carcinoma in the same studies.[97,98,102]

One of the best diagnostic performances of SII in malignancy-related outcomes appears to be testicular cancer. A very recent 2023 meta-analysis by Salazar-Valdivia *et al*. comprising 6 studies with a total of 833 patients reported that elevated SII levels indicate poor overall survival and progression-free survival (HR = 3.28; 95% CI = 1.3–8.9 and HR = 3.9; 95% CI = 2.53–6.02, respectively).[103] Although the authors summarized the significance of SII in many outcomes, they did not discuss why SII might have performed better in testicular cancer.

The diagnostic performance of the SII in cardiovascular diseases, in general, was also examined extensively. The idea behind the hypothesis of this subject is the increase of neutrophil count in endothelial dysfunction and the active role of neutrophils with platelets in the formation of atherosclerosis.[104,105] Moreover, some lymphocyte subtypes regulate inflammation and negatively affect the formation of atherosclerosis.[106]

A 2022 meta-analysis by Ye *et al*. including 13 studies and 152,996 patients reported that elevated SII levels indicate an increased risk of future cardiovascular diseases such as ischemic stroke, hemorrhagic stroke, and myocardial infarction (HR = 1.31; 95% CI = 1.06–1.63, HR = 1.22; 95% CI = 1.10–1.37, and HR = 1.11; 95% CI = 1.01–1.23, respectively).[107] In addition, studies are reporting that SII can be used as a predictor of severity in coronary artery disease and acute ischemic stroke.[108,109] Huang

et al. published a meta-analysis in 2022 with a fairly large cohort of 18.609 patients with ischemic stroke and reported that elevated SII predicts poor outcomes such as mortality and hemorrhagic transformation (HR = 2.16; 95% CI = 1.75–2.67, HR = 2.09; 95% CI = 1.61–2.71, respectively).[110] A pooled cutoff value could not be provided due to the increased heterogeneity between the studies.

The active participation of blood cells, especially neutrophils, and lymphocytes, in infectious processes implies that the SII could potentially serve as a significant biomarker for these outcomes as well. Nevertheless, a considerable number of subjects lacked meta-analyses due to the relatively lower volume of studies focusing on infective outcomes compared to other areas. A recent meta-analysis by Mangoni and Zinellu was published in 2023 and consisted of 40 studies that examine the utility of SII in predicting the disease severity, morbidity, and mortality in patients with COVID-19. In this study, the pooled sensitivity, specificity, and area under the curve of SII in predicting severe disease or mortality was reported to be 71% (95% CI = 67–75), 71% (95% CI = 64–77), and 0.770 (95% CI = 0.730–0.800).[111] In this study, the authors indicated that even though SII had a significant association with some inflammation markers (albumin and lactate dehydrogenase), no other significant association was observed in terms of inflammation markers or other known risk factors for mortality of COVID-19, meaning that SII may carry valuable information about the degree of inflammation to a potential model.

A retrospective study conducted using a large cohort of MIMIC-IV benchmark dataset with 16,007 patients with sepsis reported that SII and 28-day mortality have a J-shaped relationship (HR = 1.40; 95% CI = 1.23–1.58 for the highest quartile of SII value). In this study, the lowest risk of 28-day mortality was at the SII levels of 774.46 × 10^9/L.[112]

A prospective study with 345 patients examined the utility of SII in predicting the 28-day mortality of patients with community-acquired pneumonia and reported that the area under the curve of SII was 0.737 (95% CI = 0.672–0.802).[113] However, it is noteworthy to point out that the outcome variable of the study is 28-day all-cause mortality and not in-hospital mortality or disease severity, which can be counted as a confounding limitation.

There are limited studies on other infections or inflammation-related outcomes. In a retrospective study with 513 patients with pancreatitis, the high SII group (>755 × 10^9/L) had a significantly higher rate of 30-day all-cause mortality (HR = 2.57; 95% CI = 1.35–4.88).[114] The study did not examine the utility of SII in predicting severe acute pancreatitis or in-hospital mortality.

In conclusion, while the SII exhibited significant differences between the groups across nearly all the assessed outcome measures, its utility as a standalone test proved limited. Nonetheless, it can be inferred that SII holds significance as a biomarker due to its capacity to contribute substantial information to predictive models without inducing overfitting, especially in conditions related to malignancy. This is attributed to the consistency of its significance in numerous studies, and the fact that it is unaffected by confounding factors.

Systemic Inflammation Response Index

SIRI is an inflammatory biomarker identified in 2016 by Qi *et al*., which is calculated according to the following formula; "*SIRI = Neutrophil x Monocyte/Lymphocyte*."[115] In the original study, the SIRI was developed to identify the candidates for aggressive chemotherapy in patients with pancreatic adenocarcinoma. The idea behind the identification of this biomarker was the hypothesis that these components may have a significant impact on survival in the malignant process, which consists of immunological and inflammatory components. Numerous studies have indicated that the prognostic significance of various cancer types, including pancreatic cancer, can be assessed through parameters such as white blood cell counts consisting of neutrophils, lymphocytes, and monocytes, alongside acute-phase proteins such as C-reactive protein.[116-119] Although SIRI has been defined to be used as a prognostic marker in patients with malignancy, its diagnostic performance has been investigated in many diseases where inflammation is at the forefront.

The role of SIRI in the prognostication of malignant diseases is well-studied. All of the systematic reviews and meta-analyses about SIRI are about the diagnostic performance of the biomarker in some kind of malignancy.[120-124] In a 2021 metaanalysis that investigates the prognostic performance of SIRI in cancer patients in general which includes 10,754 cancer patients, elevated SIRI was found to be associated with short overall survival with no significant heterogeneity (HR = 2.04; 95% CI = 1.82–2.29).[120] Majority of the existing systematic reviews or meta-analyses showed similar results.[121-123]

Although SIRI has been defined to be used as a prognostic marker in patients with malignancy, its diagnostic performance has also been investigated in many diseases where inflammation is at the forefront. For example, a 2021 study investigating the diagnostic performance of SIRI in identifying ischemic stroke patients, found

SIRI was an independent predictor of 90-day all-cause mortality, even though its predictive performance was not excellent (AUC = 0.622; 95% CI = 0.598–0.645).[125] Another study in 2022 reported that SIRI was an independent predictor of poor functional outcome in ischemic stroke patients with a moderate predictive performance (AUC = 0.714; 95% CI: 0.658–0.765).[126]

A large cohort study published in 2023 which examines the performance of SIRI for all-cause death and cardiovascular mortality in 42,875 patients (patients without acute coronary syndrome) found that patients with elevated SIRI are significantly under risk of cardiovascular or all-cause death (HR = 1.39; 95% CI = 1.14–1.68 and HR = 1.39; 95% CI, 1.26–1.52, respectively).[127] Another recent study of 2023 investigating the performance of SIRI in patients with acute myocardial infarction with 4291 patients reported that SIRI was also an independent predictor of 30- and 90-day mortality with poor performance (AUC = 0.620, AUC = 0.624, respectively).[128] Another study examining the performance of SIRI in identifying acute coronary syndrome patients at high risk of a MACE also found that SIRI was an independent predictor of MACE with poor performance (AUC = 0.624).[129]

There is no extensive research about the role of SIRI in pancreatitis or cholecystitis but some very recent studies are being published. In the study of Biyik *et al*. with 332 patients with pancreatitis, SIRI was able to significantly predict severe acute pancreatitis and acute kidney injury (AUC = 0.782; 95% CI = 0.699–0.865, AUC = 0.776; 95% CI = 0.715–0.837, respectively).[130]

Based on the existing literature, it can be said that SIRI is a promising biomarker of prognostication in patients with a condition of inflammatory-dominant pathophysiology. Given its status as a relatively recent biomarker, further studies are required to achieve a more precise assessment of its diagnostic significance in cases of infectious conditions. According to the available literature, predictive performance of SIRI limits this biomarker to be used as a standalone diagnostic tool.

Delta Neutrophil Index

In the early stages of an infectious process, when the neutrophil migration to the site of infection is limited by the over-production of cytokines and chemokines, the body responds by neutrophil proliferation resulting in immature granulocytes circulating through the peripheral bloodstream.[131] Nigro *et al*. tested the prognostic performance of the immature granulocyte count in neonatal sepsis in 2005 and found it to have poor predictive power.[132] Moreover, the calculation of the immature granulocyte count was time-consuming and also showed variance depending on the observers' experience. Until 2008, the immature granulocyte count did not attract great attention. In 2008, Nahm *et al*. defined an index using immature granulocyte count; DNI.[133] DNI can be defined as the fraction of immature granulocytes amongst the myeloperoxidase-positive cells and is automatically calculated using blood cell analyzers.[134] The formula for the DNI is usually referred to as "DN = (the leukocyte subfraction assayed in the MPO channel by cytochemical reaction)– (the leukocyte subfraction counted in the nuclear lobularity channel by the reflected light beam)."[133]

There still is not extensive literature on the predictive performance of the DNI in diverse outcomes. One of the first meta-analyses and systematic reviews on DNI by Park *et al*. investigated the diagnostic and prognostic power of DNI in 2017.[135] One of the striking findings of this study is that the researchers found 12 eligible studies investigating 499 patients and 9549 control cases, which are carried out in a single center. In this study, the pooled sensitivity of the DNI for infection was found to be 67% (95% CI = 62–71), and specificity 94% (95% CI = 94–95). In the same study, the pooled sensitivity of the DNI for predicting mortality in the infected patients was found to be 70% (95% CI = 56–81) and specificity 78% (95% CI = 73–83). The authors concluded that DNI can be used as a diagnostic or prognostic tool for infectious outcomes, not as a standalone test but with other parameters such as procalcitonin.

Another meta-analysis and systematic review on DNI was published in 2018 by Ahn *et al*. investigates the value of the DNI in predicting mortality in patients with sepsis.[131] The pooled AUC, sensitivity, and specificity of DNI in predicting mortality were found to be 0.820, 70% (95% CI = 60–80), and 72% (95% CI = 68–75), respectively. The authors concluded that the DNI is more valuable in septic conditions than leukocyte count and may be a useful tool to predict sepsis severity.

We could not find any additional meta-analyses or systematic reviews in the literature that investigated the utility of DNI; the majority of the available studies were clinical in nature. Most of the studies examined the usefulness of the DNI to predict various outcomes in patients with inflammation-related diseases such as cholecystitis, pancreatitis, abscess, and Fournier's Gangrene, demonstrating similar results.[136-140] Nevertheless, given that these studies typically have a single-center focus and involve a limited number of patients, it is important to replicate these findings in diverse settings to obtain a definitive conclusion.

Conclusion

Our thorough review summarized a substantial amount of literature demonstrating significant predictive capabilities of NLR, PLR, SII, SIRI, and DNI across various inflammation-related clinical conditions and different outcomes. These parameters emerge as readily available, reproducible, and cost-effective metrics. Yet a common characteristic among these biomarkers is their limited standalone predictive performance for any given condition. Additional studies focusing on infectious processes may be warranted to obtain more precise insights about these indexes, especially about SII and SIRI. Nevertheless, these indexes offer pivotal insights by combining information from multiple variables into a single entity. This unified representation retains the essence of its components, effectively reducing the risk of overfitting in potential predictive models and aiding clinicians in making critical decisions.

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