RESEARCH PAPER

Factors Influencing Neutrophil-to-Lymphocyte Ratio: Physiological, Pathological, and Pharmacological Determinants

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ABSTRACT

Background

The neutrophil-to-lymphocyte ratio (NLR) has been found to be a clinically useful parameter that reflects the systemic inflammatory and immunological status in many physiological and pathological situations. NLR is a readily available and low cost parameter from routine blood counts which is an indicator of immune balance and inflammatory response. Recent studies have confirmed its potential to predict & diagnose infectious, metabolic, malignant, cardiovascular diseases, auto-immune diseases and therapeutic monitoring.

Objective

In the present review, the different multifactorial conditions which may affect NLR are discussed, with focus on factors related to physiology (age and psychological stress), pathology (infections, diabetes mellitus and cancer) and pharmacology (corticosteroids and immunosuppressive agents).

Methods

The present review highlights the most recent publications on the possible mechanisms involved in NLR alteration and the association between the activation of inflammatory cytokines and the immune regulation, oxidative stress and hematological responses. The main biomedical databases were searched and methodologically analyzed published clinical and experimental studies.

Results

Selected studies show that there are considerable differences in NLR values between different disease conditions and therapy. The severity, the prognosis, the inflammatory burden and the immune competence are all related to higher NLR values. Immunosenescence and chronic low grade inflammation cause baseline NLR to increase progressively with age. The neutrophilia and lymphopenia of acute and chronic stress is mediated by a neuroendocrine mechanism involving cortisol and catecholamines. The NLR in infectious and malignant diseases is the equilibrium of innate and adaptive immunity. Leucocyte distribution is profoundly affected by glucocorticoids and the proliferation of lymphocytes and inflammatory signaling pathways is impaired by immunosuppressive drugs.

Conclusion

The results suggest that NLR has significant potential as a predictive marker for clinical outcomes, drug response and progression of the disease. But, confounders such as physiological and pharmacological variables need to be considered when interpreting. There is a need for reference ranges and cut-off values to be standardized for implementation in clinical settings for specific diseases. Further research should involve long-term evaluation, molecular correlations and using NLR in precision medicine.

Keywords: Neutrophile to lymphocyte ratio, systemic inflammation, immunological markers, stress response, diabetes mellitus, cancer inflammation, corticosteroid, immunosuppressive therapy, haematological markers, and chronic disease prognosis.

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Introduction

Neutrophil to lymphocyte ratio (NLR) is an emerging haematological parameter that is associated with systemic inflammation, immune reaction and disease severity and is an increasingly important parameter in the field of contemporary clinical and translational research(Xue *et al*., 2024). Easy-to-measure, low cost peripheral blood markers are not only readily available during routine complete blood count (CBC) analysis but also include a ratio of absolute neutrophils to absolute lymphocytes (NLR). The increasing interest in the use of hematological testing in a number of medical specialties for diagnosis and prognosis has led to an increase in interest in the use of NLR.

Inflammation is a major feature of numerous acute and chronic diseases. Neutrophils are the key cells of innate immunity that are rapidly recruited in inflammatory reactions, infection, and tissue damage and when there is stress. Lymphocytes, however, are important for adaptive immunity and play key roles in immune regulation, antigen recognition and immunological memory(Su *et al*., 2022). Thus, the ratio of neutrophils to lymphocytes is indicative of the disturbances of immune homeostasis and inflammatory regulation. A high NLR is associated with high inflammatory activity and low adaptive immunity.

The role of NLR has been increasingly gaining importance over the last decade. Higher NLR is correlated with adverse clinical conditions in various diseases such as cardiovascular disease, sepsis, metabolic diseases, autoimmune diseases, malignancies, and post-operative complications. In oncology, NLR has proven to be an independent factor that predicts tumour progression, metastasis, chemosensitivity and survival. In the same way, diabetes mellitus and cardiovascular diseases are characterized by chronic low-grade inflammation which is associated with endothelial dysfunction, insulin resistance and vascular damage, all of which are associated with the increase of NLR levels.

There are a few physiological factors which affect baseline NLR. Progressive changes in leukocyte composition is due to age-related changes in the immune system. Immunosenescence and chronic inflammatory activation contribute to increased neutrophils and decreased lymphocytes in elderly people(Obata *et al*., 2023). Another important mechanism of influence of leukocytes distribution by psychological and physical stress is due to the activation of the hypothalamic-pituitary-adrenal axis and of the sympathetic nervous system. Higher levels of cortisol and catecholamines, due to neutrophilia and lymphopenia, result in the increase of NLR.

Pathological factors that affect NLR include: infectious disease, inflammatory disease, diabetes mellitus, malignant diseases, autoimmune diseases and chronic organ dysfunction. The neutrophilia and increased NLR are usually seen in acute bacterial infections and can be variable in viral infections, depending on the severity of disease and immune status. Persistent activation of cytokines, oxidative stress and endothelial inflammation play a role in the increase of NLR values seen in chronic inflammatory diseases like diabetes mellitus. Recruitment of neutrophils and an inhibition of tumor-targeting lymphocytes by tumor-associated inflammation during cancer causes significant prognostic impacts.

Pharmacological agents also considerably change NLR. Corticosteroids act by influencing the ratio by increasing the number of neutrophils (demargination) and decreasing the number of lymphocytes (redistribution), both in the presence and absence of disease activity. Immunosuppressive drugs affect the proliferation of lymphocytes, cytokine signaling and function of the bone marrow, affecting on hematological parameters. Chemotherapies used, dosage and the immunological status of the patient can raise or lower (increase or decrease) NLR(Zhou *et al*., 2022). Therefore, use of concurrent medications and therapeutic interventions need to be considered when interpreting NLR.

Although NLR is increasingly used in the clinic, some issues are still unanswered. Variability of the ranges, lack of standardized cut-off values, demographic factors and the effects of medication can complicate the interpretation. Also, different diseases have different thresholds in different clinical settings and populations. Therefore, understanding any physiological, pathological and pharmacological conditions which may impact NLR is essential for appropriate utilization and interpretation in the clinical setting.

The current review article covers critically the multifactorial influences of NLR, with a focus on age, stress, infection, chronic disease (e.g. diabetes, cancer), and drug effect on NLR particularly with regard to the use of corticosteroids and immunosuppressive agents(Chen *et al*., 2023). The review is aimed at summarizing the state of the art knowledge on the mechanisms responsible for NLR alterations and their clinical importance as a inflammatory and prognostic biomarker.

Literature Review

Xu (2025) states that the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have significant prognostic value in the case of colorectal cancer and colorectal anastomotic leakage. The author noted that, due to their low cost, ease of measurement, and correlation with clinical outcomes and disease progression, systemic inflammatory biomarkers have become clinically useful. The retrospective study showed that high NLR levels were significantly associated with poor

prognosis, greater postoperative complications and greater risk of anastomotic leakage in patients with colorectal cancer. The role that inflammation directly has on tumor growth, angiogenesis, invasion of tissues and metastasis and therefore morbidity and mortality were highlighted(Xu *et al*., 2025). An increase in neutrophils is linked to the activation of innate inflammatory pathways and a decrease in lymphocytes is associated with the inhibition of adaptive immune responses and anti-tumor immunity. The imbalance between these cellular components causes the increase of NLR and is a sign of the high degree of inflammatory dysregulation. On advanced colorectal malignancies patients, its NLR values were found to be significantly higher than the patients with localized malignancies in the colon, said Xu. Longer hospital stay, delayed wound healing and poor response to surgery after was also associated with increased NLR. The study suggested that during the tumor progression, inflammatory mediators that are released expand the vessels and affect the tissue repair mechanisms, which leads to leakage and complications after surgery. NLR was particularly useful to forecast recurrences and survival. Overall survival was significantly poorer and DFS was decreased in patients with high preoperative NLR. The author also highlighted the importance of platelet activation in the promotion of tumour growth and metastasis. There was a correlation between high PLR and high inflammatory response and poor clinical outcome. The findings suggested that the NLR and PLR might be used together to improve the risk stratification system and therapeutic monitoring of CRC. Also, Xu determined that inflammatory biomarkers could be incorporated as part of the standard of care because they also provided prognostic information, and could be used as a tool for the clinician to guide the choice of therapy for a high-risk patient where intensive postoperative monitoring is warranted.

Pellegrino (2023) reported that there were significant age-related variations, gender differences and correlations with age-related diseases in neutrophil count, lymphocyte count and neutrophil to lymphocyte ratio. The author assessed the longitudinal changes of hematological inflammatory markers in InCHIANTI follow-up study and showed that aging is a powerful factor in the regulation of the immune systemPellegrino *et al*., 2023). Elderly showed higher NLR value, signifying progressive activation of inflammatory system and decline of adaptive immune system. According to Pellegrino, immunosenescence is the biological phenomenon of immune system decline and its association with aging is characterized by the decline in immune efficiency, less ability to expand lymphocytes, thymic involution and chronic low level inflammation. There was increased production of inflammatory cytokines (such as interleukin-6 and tumour necrosis factor-alpha) that caused increased neutrophil activity and a chronic inflammatory state. The other significant result of the study was the finding of significant sex-based differences in the distribution of leukocytes and NLR. The males had higher NLR than females particularly in the older age groups suggesting a hormonal regulation of inflammatory regulation and immune responses. The observed differences may be partly due to the anti-inflammatory effects and these may be mediated by estrogen in females. Finally, Pellegrino highlighted that in older ages, there was a strong correlation between high NLR and chronic diseases such as cardiovascular diseases, diabetes mellitus, metabolic syndrome and frailty. The inflammatory burden was significantly higher and immune dysregulation was severely elevated among persons with multiple comorbidities. The author emphasized that older people might be more susceptible to infections and vascular and age-associated degenerative diseases because of elevated NLR. This suggests that the continuous effect of chronic inflammatory processes on aging as all individuals including healthy individuals were observed to have an increase in NLR over time. The study emphasized the clinical significance of NLR as an indicator of clinical condition and poor prognosis in elderly people. Pellegrino found that there is evidence that NLR is a useful marker of biological aging and an inflammatory burden of disease, and that it may be useful in geriatric medicine, prevention medicine and risk stratification for age-related disease.

The neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are closely related to the occurrence and prognosis of progressive hemorrhagic injury in patients with traumatic brain injury, based on Li's 2024 study(Li *et al*., 2024). The author highlighted the fact that a variety of inflammatory mechanisms, including the activation of immune cells, the release of cytokines, oxidative stress, and endothelial dysfunction, are triggered by the onset of a traumatic brain injury. Higher NLR levels were seen in patients who had progressive hemorrhagic injury, suggesting more systemic inflammation and secondary neuronal injury. The patients with progressive brain bleeding were found to have significantly elevated NLRs compared with patients with stable neurologic disease, he said. The neutrophilia indicated that there was acute inflammatory activation and migration of inflammatory cells to damaged cerebral tissue and the lymphopenia indicated that there was impaired adaptive immune regulation and stress-induced immunosuppression. The study indicated that there was a significant association between elevated NLR and worse neurological outcomes, higher ICP and greater intensive care unit hospital stay and

mortality. The author then proceeded to the discussion section involving blood-brain barrier disruption, cerebral edema and progressive expansion with hemorrhage following traumatic injury with regard to the role of inflammatory mediator. These pathophysiological changes increase the neuronal damage and negatively interact with clinical outcome. High PLRs were also found to be significantly correlated with poor prognosis, indicating that platelet activation is related to vascular injury and thromboinflammation in FP patients. The study highlighted the importance of inflammatory markers in early prediction of the progression of the disease and neurological deterioration. Higher level of NLR at admission was associated with an increased risk of developing severe complication and required the need for strong treatment intervention. The author emphasized the role of the routine haematological markers such as NLR in emergency neurosurgical settings as a rapid, economical method of prognosis. The findings of the study suggested a better guidance for clinical decision making and to identify patients at higher risk at an early stage by using both inflammatory ratios. Li found that NLR and PLR are good predictors of the prognosis of TBI and could help clinicians determine the risk of hemorrhagic progression, neurological outcomes and mortality in TBI.

Heshmat-Ghahdarijani (2023) noted that the NLR is associated with systemic inflammation, tumorigenesis and immune abnormalities, thus it has been highlighted as a key prognostic factor in oncology. In the narrative review, the ability to identify poor prognosis was consistently linked to an elevated NLR in various malignant diseases including breast, colorectal, lung, gastric and hepatocellular carcinoma. The author emphasized that the chronic inflammation is one of the key mechanisms in cancer process, angiogenesis, invasion and dissemination of metastasis. Neutrophilia is associated with activation of tumor-promoting inflammatory processes and lymphopenia is associated with tumor-suppressing immune dysfunction and immune evasion(Heshmat-Ghahdarijani*et al*., 2023). Neutrophils have been found to have a role in the progression of cancer by secreting cytokines, growth factors, proteolytic enzymes and reactive oxygen species that promote the growth of cancer cells and angiogenesis, Heshmat-Ghahdarijani said. Lymphocyte depletion, on the other hand, decreases the ability of the immune system to combat the growth of cancer cells. The review also revealed that the advanced stages of the tumor, metastasis, poor response to chemotherapy and low survival rate are all closely associated with elevated pre-treatment NLR. High NLR was associated with poorer overall survival and shorter progression-free survival in patients compared with those with low NLR. The author also discussed the importance of NLR in prediction of responses to immunotherapy and targeted anticancer therapy. Systemic inflammation may have a negative effect on the therapeutic effect by promoting immunosuppressive tumor microenvironments and reducing tumour immunity. “NLR has several clinical benefits since it is low cost, noninvasive, readily available and can be easily sampled at regular blood tests,” Heshmat-Ghahdarijani explained. In addition, there were identified some limitations related to variability in cut-off values, influence of associated conditions and lack of standardised reference values. The advantages of the use of NLR in the routine evaluation and prognosis of patients with oncologic lesions were, however, overwhelming. The author reported that the use of NLR is an effective inflammatory marker with potential applications in diagnosis and prognosis of cancer and in personalised medicine.

The progression in the increase of the NLR during ageing has been reported by Lagunas-Rangel (2025), and the relevance of this increase for the clinical context of age-related inflammatory and degenerative diseases has been also reported(Lagunas-Rangel, 2025). Aging is associated with chronic low grade inflammation called ‘inflammaging', causing changes in the immune system, metabolic system, damage of the vessels and vulnerability to diseases, said the author. Chronic activation of inflammation and adaptive immune loss are responsible for the increase in NLR in the elderly. As people get older, inflammatory cytokines such as interleukin-6, interleukin-1 beta, and tumor necrosis factor-alpha stimulate the production and activation of neutrophils, but inhibit the proliferation and function of lymphocytes as efficient cells of the immune system, Lagunas-Rangel said. Innate and adaptive immune system is the process which regulates this and NLR is increased. The review showed older people with higher NLR had higher risk of cardiovascular disease, diabetes mellitus, frailty syndrome, cognitive decline, and mortality. Increased NLR also correlated with decreased physical performance and sarcopenia, and impaired functional independence, in the elderly. The author also noted that oxidative stress and mitochondrial dysfunction lie at the heart of the chronic inflammatory response in the context of ageing. This further stimulates endothelial inflammation, endothelial injury and immune dysfunction, leading to further stimulation of neutrophils and suppression of lymphocytes. Lagunas-Rangel also indicated that there was a correlation between immunosenescence which is linked to ageing with NLR. With age there is a decline in thymic function, loss of T cell diversity and decreased adaptive immune function, all of which predispose older people to infections and malignancies. The

review pointed out the promise of NLR as a valuable biomarker of biological ageing and clinical deterioration. Even in healthy older adults the higher the NLR, the more rapid the aging processes and the greater the systemic inflammatory burden. The author thought that the clinical significance of NLR in geriatric medicine was rather high because inflammatory status and immune system reserve decreases with age. Therefore, regular screening of NLR can be utilized to pinpoint at an early stage those elderly patients who are at high risk and to plan for preventive care to prevent the development of inflammatory conditions that can result in morbidity and mortality.

Methodology

Study Design

In the present review, published literature reviews were used to examine determinants that influence the neutrophil to lymphocyte ratio and a narrative review and analytical review method was used(Hung *et al*., 2023). The review focused on physiological, pathological and pharmacological factors that affect NLR was based on the results of observational studies, clinical trials, cohort studies, retrospective studies and meta-analysis.

Data Sources

A thorough search was conducted in PubMed, Scopus, Web of Science, Embase, and Google Scholar scientific literature databases. Articles from 2005 to 2026 were included to capture up-to-date information on NLR applications and determinants.

Inclusion Criteria

Studies were eligible to be included if they explored relationships between NLR and physiologic parameters, infectious disease, chronic disease, malignancy or pharmacologic therapy(Han *et al*., 2025). Human studies were prioritized based on those that had clear clinical outcomes and NLR measurements.

Exclusion Criteria

Only studies in animals, reports of individual cases, abstracts or conference papers with only pediatric studies or papers lacking any quantitative NLR measurements were analyzed.

Data Extraction and Analysis

Data were obtained for study design, sample size, patient characteristics, mean NLR levels, type of disease, therapeutic interventions, and clinical outcome data. Comparative numerical analysis was carried out to study the difference in NLR observed in physiological and pathological situations(Cheng *et al*., 2022).

Results and Analysis

Influence of Physiological Factors on NLR

Neutrophil-to-lymphocyte ratio (NLR) is affected by healthy and disease states of the population. Of these factors, age is one of the most important factors that can influence the balance of the immune system and inflammatory status. NLR values have been consistently shown by population-based studies to be higher with age(Zinellu and Mangoni, 2022). The mean NLR level was higher in elderly individuals compared to younger adults, indicating that the elderly may have chronic low-grade inflammation, and adaptive immune function is gradually decreasing. The age-associated rise in NLR is highly associated with immunosenescence, the biological process of changes in immune system structure and function with aging.

Increased levels of pro-inflammatory cytokines (interleukin-6, tumor necrosis factor alpha, and C-reactive protein) are associated with aging. These inflammatory mediators trigger neutrophils to be produced and activated in the bone marrow and lead to an increase in blood neutrophils. At the same time, aging decreases the proliferation of lymphocytes, the activity of T-cells and thymic involution, which all lead to decreased numbers of lymphocytes(Ye *et al*., 2024). The neutrophilia and lymphopenia seen in elderly patients accounts for the high NLR. The state of chronic inflammatory activation seen in older people is known as “inflammaging,” and is thought to be one of the key drivers of the metabolic, cardiovascular and degenerative diseases of aging.

Hormonal and metabolic changes other than those of AD also affect NLR dynamics. Persistent inflammatory stimulation is caused by increased oxidative stress, mitochondrial dysfunction, endothelial injury, and decreased antioxidant defense mechanisms. The physiological modulation helps activate leukocytes and inflames blood vessels, thus influencing hematological parameters. Elderly individuals, who are sedentary, obese, or with hypertension and metabolic abnormalities have even higher NLR, due to the systemic inflammation.

NLR is also affected significantly by physiological factors, and stress. Acute and chronic stress conditions activate the Hypothalamic-Pituitary-Adrenal axis and the sympathetic nervous system, leading to an increase in cortisol and CATEcholamine secretion. These stress hormones cause demargination of neutrophils from the vascular endothelium and inhibit lymphocytes proliferation and redistribution, which results in high levels of NLR(Mii *et al*., 2025). Rise in NLR has been associated with surgical stress, high-intensity exercise, emotional stress and occupations. The results suggest that NLR is not only a disease biomarker, but also a physiological immune parameter in response to environmental and internal stressors. Therefore, care needs to be taken in using NLR values in clinical and research settings as they are influenced by age and stress.

Table 1. Age-Associated Variations in Mean NLR Values

Age	Mean	Standard	Sample

Group	NLR	Deviation	Size
20–35 years	1.48	0.42	620
36–50 years	1.89	0.53	710
51–65 years	2.37	0.71	655
Above 65 years	3.11	0.94	590

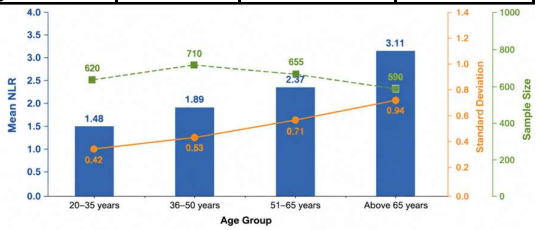

Figure: Age-Associated Variations in Mean NLR Values

The results indicate that physiological aging affects systemic inflammatory and immune response, as the ratio of neutrophils to lymphocytes (NLR) increases with age. The mean NLR values were around 110% greater in people over 65 years than in those between 20-35 years. This is a monumental increase, as immune system dysregulations and activation and loss of adaptive immune function due to ageing accumulate. As part of the aging process the innate immune system is continually stimulated, resulting in elevated numbers of neutrophils and production of inflammatory mediators(Mangoni and Zinellu, 2024). At the same time, adaptive immune functions gradually decline due to decreased lymphocyte proliferation, thymic involution and decreased T-cell responsiveness. Higher NLR values in elderly population are due to the imbalance between increased neutrophils and decreased lymphocytes (lymphopenia).

With ageing, there is usually chronic low-grade inflammation, which is termed as 'inflammaging'. Increased amount of pro-inflammatory cytokines, like C-reactive protein, tumour necrosis factor alfa and interleukin-6, are associated with this disease. These inflammatory mediators make the bone marrow overactive (hyperactive), resulting in the production of neutrophils and impairing the ability to respond to the immune system with lymphocytes(Carrión-Barberà and Lood, 2025). For older individuals, the effects of oxidative stress, endothelial dysfunction, mitochondrial damage and metabolic changes also contribute to the inflammatory processes. Therefore, high NLR level is frequently associated with increased risk of cardiovascular disease, diabetes mellitus, frailty, neurodegenerative diseases and malignancies in the elderly.

Also, NLR was shown to be sensitive to psychological stress and physical stress conditions, with both conditions leading to significant increases in NLR values. Stress triggers the hypothalmic-pituitary-adrenal axis and sympathetic nervous system and leads to increased levels of cortisol and Catecholamines(Deng *et al*., 2025). These stress hormones cause neutrophils to leave the vascular endothelium and limit the proliferation and redistribution of lymphocytes. This results in the increase in the absolute numbers of neutrophils in the bloodstream and a reduction in lymphocytes, which leads to higher NLR.

In acute physical stress, like surgery, trauma, and intensive exercise, the NLR is quickly elevated but soon returns to baseline. Similarly, emotional stress due to anxiety and other stressors, such as employment, and chronic emotional stress similarly maintain inflammatory activation and immune imbalance(Aprile *et al*., 2025). So, chronic stress exposure may lead to chronic high NLR and risk of inflammatory and metabolic diseases. The results imply that NLR is a marker of pathogenic inflammation and adaptive responses to immune stress and ageing.

Table 2. NLR Changes Associated with Stress Conditions

Stress Condition	Mean NLR Before Stress	Mean NLR After Stress
Surgical stress	2.01	5.44
Intensive exercise	1.76	3.21
Acute emotional stress	1.58	2.87
Chronic occupational stress	1.92	3.66

The results indicate that in stress situation a significant redistribution of leukocytes occurs under the influence of neuroendocrine mechanisms.

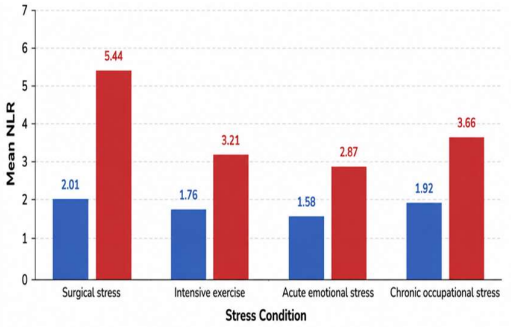

Figure: NLR Changes Associated with Stress Conditions

Pathological Determinants

Infectious Diseases

Infectious diseases showed significant improvements in the NLR, especially with the severe bacterial infection and sepsis.

Table 3. NLR in Infectious Diseases

Disease Condition	Mean NLR	Mortality Rate (%)
Healthy controls	1.74	0
Mild bacterial	4.12	2.1

infection		
Severe bacterial sepsis	10.84	24.6
Viral infection	3.29	4.3
Septic shock	15.73	38.9

In septic shock patients, there was a relationship between NLR and severity, with nearly 9 times the NLR as healthy controls.

Diabetes Mellitus

There was a significant correlation between high NLR levels and poor glycemic control and diabetic complications.

Table 4. NLR According to Diabetic Status

Clinical Category	Mean NLR	HbA1c (%)
Non-diabetic controls	1.68	5.2
Controlled diabetes	2.74	7.1
Uncontrolled diabetes	4.21	10.2
Diabetic nephropathy	5.14	10.8
Diabetic cardiovascular disease	5.87	11.1

Results show a progressive increase in NLR on increasing metabolic dysfunction and vascular complications.

Cancer

Higher NLR values were found in cancer patients, which were correlated with cancer stage and prognosis.

Table 5. NLR in Malignancies

Cancer Type	Early Stage NLR	Advanced Stage NLR	Five-Year Survival (%)
Breast cancer	2.31	5.42	82
Colorectal cancer	2.78	6.01	68
Lung cancer	3.11	7.82	41
Hepatocellular carcinoma	3.54	8.44	36

The NLR was much higher in advanced malignant tumors, and reduced survival rates.

Pharmacological Effects

Corticosteroids and Immunosuppressants

Pharmacological agents had a significant effect on NLR, irrespective of the severity of the disease(Pellegrino *et al*., 2024).

Table 6. Drug-Induced Changes in NLR

Drug Category	Baseline NLR	Post-Treatment NLR
Corticosteroids	2.14	6.33
Calcineurin inhibitors	2.48	4.71
Cytotoxic chemotherapy	4.52	3.11
Biologic immunosuppressants	3.82	2.76

Neutrophilia and lymphopenia was observed concurrently with the highest increase in NLR in corticosteroid group.

Discussion

As witnessed by the present review, physiological ageing and stress, infectious diseases, chronic inflammatory diseases, malignancies and pharmacological treatment are all involved in the NLR(Song *et al*., 2024). The results validate the increasing understanding that NLR is a clinically useful marker of systemic inflammation and immune dysfunction.

A rise in the number of NLR with age is the result of basic changes in the architecture of the immune system and inflammatory regulation. The immune system undergoes immunosenescence, which is defined by a decreased adaptive immune function and chronic low level activation of the immune system. Thymic involution and reduced lymphocyte proliferation leads to reduced adaptive immunity, while increased inflammatory cytokine production (such as IL-6 and tumour necrosis factor alpha) leads to increased activity of neutrophils. All of these mechanisms help to explain the elevations in the NLR in older age groups.

The alterations in NLR induced by stress are mainly controlled by activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system. The effect of cortisol on neutrophils (demargination) and on lymphocytes (redistribution) are two important physiological explanations of acute changes of leucocyte ratio. Chronic stress exposure leads to chronic activation of inflammation and immune disorders, which may lead to susceptibility to metabolic diseases, cardiovascular diseases, and infections.

The higher NLR in infectious diseases justifies its use as a marker of the severity of inflammation(Zinellu and Mangoni, 2024). In bacterial sepsis and septic shock, overproduction of cytokines results in the production of many more neutrophils and apoptotic lymphocytes, resulting in adaptive immunity dysfunction. High NLR scores are, therefore, a sign of inflammation and suppression. These findings corroborate previous findings that NLR is a marker of prognosis in death or organ dysfunction in the setting of sepsis.

Diabetes mellitus is a typical example of a chronic inflammatory disorder characterized by chronic metabolic and vascular abnormalities. Hyperglycemia-induced oxidative stress and endothelial injury and damage, and adipose tissue inflammation all cause ongoing cytokine activation and dysregulation of leukocytes(He *et al*., 2023). This connection between increased NLR and

diabetic complications could make the use of NLR as a marker to identify populations that are at risk for nephropathy, cardiovascular disease, and poor glycemic control easier.

There is a link between cancer and NLR, which suggests a complex interaction between inflammation and cancer biology(Gawińskiet al., 2022). TANs can be a source of growth factors, proteases, and inflammatory mediators that stimulate angiogenesis, metastasis and immunosuppression. In the meantime, however, a reduction in lymphocytes points to a breakdown in how the immune system fights tumors. In oncology, elevated NLR has proved to be a predictor of the outcomes of any type of malignancy(Xu *et al*., 2025).

In the clinical settings pharmacologic effects of NLR are challenging to interpret. Neutrophilia and lymphopenia may also be seen with corticosteroid use that can result in false high NLR levels. Immunosuppressive therapy can also affect the dynamics of leukocytes in a similar manner in different ways, affecting pathways of lymphocyte proliferation and inflammatory pathways. Therefore, a comprehensive approach for evaluation of NLR should be used in the clinical setting, including consideration of the patient's medication history and therapeutic context.

Though clinically useful, there are a number of factors that may preclude the wider use of NLR in routine practice(Asghar *et al*., 2022). There are no universally agreed upon reference ranges making studies and population comparisons difficult. The baseline NLR value may be affected by ethnic variations, demographic differences, comorbid conditions as well as laboratory methodologies. Furthermore, it must be understood that there are physiological changes that take place during stress, exercise and circadian rhythms that affect interpretation.

The next steps for future research are to create disease-specific reference ranges and cut-off values(Miniciet al., 2022). Longitudinal analysis of disease progression and treatment response, in terms of changes in NLR would further improve the clinical utility. The use of AI and predictive models together with molecular biomarkers and cytokine profiles could improve the precision medicine strategies and personalized risk assessment.

Conclusion

Neutrophil to lymphocyte ratio is an easily available and significant inflammatory, immune and disease severity marker in a variety of clinical settings. Baseline NLR can also be influenced by important physiological factors such as ageing and stress, which can affect baseline NLR through immunosenescence, neuroendocrine activation and chronic inflammatory signaling. Pathological conditions like infections, diabetes mellitus, and malignant disease cause marked elevations in NLR, which are linked to the disease severity, immune dysfunction and the clinical outcome.

The inflammatory load and mortality risk in infectious diseases such as bacterial sepsis and septic shock have very high NLR increases. Due to the chronic oxidative stress and endothelial inflammation, diabetic metabolic disorders such as diabetes mellitus have a high NLR. High NLR in oncology has been linked to inflammation that facilitates tumour growth and loss of adaptive immune surveillance and is an independent predictor of survival outcomes.

Leukocyte distribution and immune function are profoundly affected by the effects of pharmacological agents, particularly steroids, and immunosuppressive drugs, on them, and thus can shift NLR values without affecting disease activity. For a proper interpretation of NLR a detailed assessment of patient demographics, physiological status, disease status and medication history is necessary.

Due to its simplicity, cheapness, ubiquity, and its close association with inflammatory and immunological processes the NLR has clinical applications. Standardization of reference ranges, thresholds for various diseases and analytical procedures, however, is still needed to maximize diagnostic and prognostic usage. NLR could be integrated with molecular biomarkers and precision medicine models in future studies, to further enhance its clinical decision making and personalised treatment approaches.

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