Narrative review

Neutrophil-To-Lymphocyte Ratio In Patients With COVID-19 Infection: A Narrative Review

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Abstract

Coronavirus disease 2019 (COVID-19), a contagious illness, has been quickly spreading throughout the world and continues to pose a danger to public health on a worldwide scale. It is essential to diagnose potentially serious or critical patients immediately and provide targeted patients with prompt therapy because patients with critical or severe cases have poor prognoses. Current biomarkers cannot reliably predict the severity of COVID-19 infection; thus, we need surrogate indicators to determine the severity of COVID-19 and forecast its progression. The neutrophil-to-lymphocyte ratio (NLR) is a new biomarker that has been linked to inflammation and prognosis in a variety of diseases. In this narrative review, we investigated the NLR's diagnostic and prognostic validity in patients with COVID-19 infection.

Keywords: Neutrophil-to-lymphocyte ratio, COVID-19, Coronavirus, Diagnosis, Prognosis

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Introduction

In December 2019, a number of pneumonia cases of unknown origin appeared in Wuhan, Hubei Province, China (1). For the first time on January 7, 2020, the China Center for Disease Control and Prevention identified a new strain of the coronavirus, known as SARS-CoV-2 or 2019-nCoV (1). The World Health Organization (WHO) called this highly contagious viral infection Coronavirus 2019 (COVID-19), which spread rapidly worldwide and became a pandemic on March 11, 2020 (2). Despite unprecedented restrictions such as social distancing imposed by governments, the prevalence of the disease has not yet been controlled, it has spread very quickly and affected all ages, even newborns (3,4).

SARS-CoV-2 is a single-stranded RNA virus that belongs to the β-coronavirus family, which contains the other two coronaviruses, Middle East Respiratory Syndrome Corona Virus (MERS-CoV) and Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV), which has caused deadly infections over the past two decades (5,6). Compared to the previous coronavirus outbreaks, SARS-CoV-2 has the same pattern of infection and clinical manifestations but has a much higher transmission rate (7,8). On the other hand, transmission from asymptomatic patients (9), aerosols (10), as well as staying up to 7 days on surfaces (10), has hampered efforts to prevent the spread of COVID-19.

The main clinical manifestations of COVID-19 infection are fever, myalgia, dry cough, sputum production, fatigue, dyspnea, and headache (11,12). Studies demonstrated that patients with advanced ages, obesity, and comorbidities, including hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, and cancer have poorer prognosis (13,14).

Clinical signs and symptoms of patients with COVID-19 infection categorized into four stages based on the clinical severity (Table 1) (15). Although most patients develop the mild or moderate disease, 15% of patients suffer from a severe disease that requires oxygen therapy and hospitalization, and 5% also develop critical diseases that are accompanied by complications such as acute respiratory distress syndrome (ARDS), thromboembolism, sepsis, liver damage, cardiac injury, renal failure, shock, and multiple organ failure (16). Besides, Children with COVID-19 infection typically show limited symptoms, but some children reveal severe conditions that have an inflammatory syndrome that includes symptoms that resemble Kawasaki disease (17–19). Furthermore, patients with a severe COVID-19 infection are at increased risk for opportunistic fungal infections, such as mucormycosis and pulmonary aspergillosis, which may affect multiple organs and cause mortality (20,21). Therefore, it is important to identify severe or critical cases in a timely manner and provide appropriate treatment for them as soon as possible, which can result in a better prognosis and a lower readmission rate (22).

To date, the diagnosis of COVID-19 infection is based on nucleic acid detection using real-time Polymerase Chain Reaction (PCR). However, the false-negative results and shortage of diagnostic kits caused most patients cannot be identified timely (23). Also, radiological evaluation such as chest computed tomography (CT) scan has a crucial role in COVID-19 diagnosis, but the imaging results of a chest CT scan might vary widely and significantly from patient to patient (24-25).

The world urgently needs alternative criteria to identify COVID-19 infection due to the pandemic's rapid spread. Appropriate predictors may assist in predicting disease severity and progression in order to contribute to clinical care, screening, and the avoidance of fatal consequences. On the other hand, it is challenging to predict severe COVID-19 status using commonly used laboratory indicators such as IL-6, D-dimer, hemoglobin, eosinophil, platelet, transaminase levels, activated partial thromboplastin time, prothrombin time, and lactate dehydrogenase (11,26–29). Moreover, in order to reduce morbidity and mortality, patients

with severe COVID-19 infection must be evaluated for hyper-inflammatory conditions utilizing laboratory markers due to the fact that various studies have revealed that some of these patients may have immune dysregulation that could contribute to the emergence of a virally induced hyper-inflammatory condition (30). Cytokine profile assessments are not regularly undertaken in the majority of laboratories; however, routine white cell differentials and full blood counts are commonly accessible and conducted in most healthcare facilities caring for patients with COVID-19 (31). Consequently, accurate indicators of infection like the neutrophil-to-lymphocyte ratio (NLR) may be useful in efforts to assist in diagnosis and prognosis.

The significance of NLR in patients with severe and non-severe COVID-19 infection has been examined in some studies. Therefore, we carried out this narrative review to comprehensively assess the evidence supporting the effectiveness of NLR in COVID-19 management.

Neutrophil-to-lymphocyte ratio

The NLR, which is determined as the absolute neutrophil count divided by the absolute lymphocyte count in peripheral blood, is a novel inflammatory biomarker that links the innate immune response, which is predominantly supported by neutrophils, with adaptive immunity, which is supported by lymphocytes (32,33). Neutrophils represent the first layer of defense for the host towards pathogens throughout of a variety of processes such as phagocytosis, chemotaxis, the development and release of cytokines, and release of reactive oxygen species (34).

Although NLR is a sensitive hematologic indicator, it has less specificity to evaluate the intensity of inflammation or infection, stress, and severity of disease of several origins (35,36). NLR represents activity of the vegetative nervous system as well as immune-inflammatory response. The connection between the brain and the immune system is provided by the sympathetic nervous system, which stimulates lymphoid organs and releases hormones (37).

The activity of the vegetative nervous system affects two primary groups of leukocytes: granulocytes and lymphocytes. Stress hormones and sympathetic activation increase the quantity and activity of neutrophils, while parasympathetic activity and cortizol regulate the performance and distribution of lymphocytes, resulting in a decrease in the number of lymphocytes in peripheral blood. Leukocytosis and neutrophilia are induced by the sympathetic nervous system's activation, which also results in an increase in the NLR (38,39).

As a result, NLR is an inflammatory indicator that represents systemic inflammatory responses and has been evaluated in patients with rheumatoid arthritis, sepsis, cardiovascular disease, pneumonia, cancer, multiple sclerosis, ankylosing spondylitis, familial Mediterranean fever, and pregnancy complications (40–50).

The critical diagnostic and prognostic function of NLR in infections has become clear as a result of accumulating research. In a study by Han et al., NLR was more accurate than the lymphocyte count, neutrophil count, and total leukocyte count and is employed as an effective diagnostic tool to screen people for influenza virus infection (51). NLR has also been quantified and used to predict recurrence in hepatitis B patients (52).

NLR physiological values

As mentioned before, calculating NLR values involves dividing the absolute neutrophil count by the lymphocyte count. There is disagreement on its normal cut-off value (53–55). In a large retrospective investigation, Forget et al. found that healthy adults in a non-geriatric adult population could have normal NLR levels between 0.78 to 3.53 (55).

According to another research, the median NLR for the general population was 1.76, with limits of 2.5% at 0.83 and 97.5% at 3.92. Furthermore, the mean NLR was greater in men compared to women (1.88 and 1.68, respectively) and in old

adults compared to those aged 45 to 54 years (2.13 and 1.63, respectively) ($p< 0.001$) (56).

According to the study by Karakonstantis et al., there are some factors which might assess a false increase in NLR, including endogenous sexual hormones, exogenous steroid intake, age, HIV, and active hematological disorders (57).

NLR application in viral infection

Numerous investigations have looked for biomarkers that can distinguish between viral and bacterial infections. Holub et al. evaluated the NLR's potential to discriminating between viral and bacterial infections (54). They evaluated the NLR value in 24 patients with viral infection, 45 patients with bacterial infection, and 18 healthy individuals. The medians of NLR for healthy controls were 1.86, for viral infections they were 2.86, and for bacterial infections they were 11.73 (54). For bacterial infection, the NLR cut-off value of 6.2 demonstrated specificity values of 0.96 and sensitivity values of 0.91. These findings point to the possibility of NLR as a diagnostic tool to distinguish between bacterial (NLR> 6.2) and viral infection (NLR< 6) (54).

In another investigation, the potential of NLR to distinguish between several adult patient groups treated for fever was examined (58). A total of 299 patients makes up the cohort, including 14 patients who had viral infections, 150 patients had microbiology and serology-confirmed bacterial infections (27 had septicemia, 30 had urinary infection, and 69 had pneumonia), and 9 patients had infectious mononucleosis. They found that the mean NLR for viral infection was 2.41, the median was 0.63, and the mean NLR for bacterial infection was 12.23, the median was 7.94 (58).

NLR and the pathophysiology of COVID-19 infection

It is currently well understood that lymphocyte reduction precedes the beginning of COVID-19 infection and that the rate of this decrease is negatively correlated with the severity of the disease (59). Particularly, T and NK cells, which seem to be essential for controlling viral infection, were significantly reduced, whereas B cells were at the lower end of their normal range (30). CD8+ T cells and NK cells function is impaired in COVID-19 patients, as well as their quantity. The expression of the inhibitory receptor NKG2A is thought to be upregulated in individuals with COVID-19, which appears to be one of the causes (60). It should be noted that NKG2A is an inhibitory receptor that is significantly expressed by cytotoxic lymphocytes like CD8+ T cells and NK cells (61).

Notably, after treatment, COVID-19 patients' NK and CD8+ T cell numbers were recovered, and NKG2A expression was downregulated. These findings demonstrate that the acute phase of COVID-19 infection is linked to the functional exhaustion of cytotoxic lymphocytes (60). In contrast, in severe cases in comparison to mild-to-moderate cases, the proportion of naive T helper cells was elevated while memory T helper cells decreased (30).

According to a study by Zheng et al., the reduction of antiviral immunity in patients with COVID-19 is caused by a continuous decrease in the number of TNF-α+ NK, IL-2+ NK, IFN-γ+ NK, and CD107a+ NK cells and the mean fluorescence intensity of granzyme B+ NK cells (60). These findings were supported by the observation that patients with COVID-19 had lower percentages of IL-2+CD8+, IFN-γ+CD8+, and CD107a+CD8+ T cells and the mean fluorescence intensity of granzyme B+CD8+ T cells than healthy subjects (60). In addition, the IFN-γ defense mechanism was compromised, which meant that it did not prevent the formation of pathogenic neutrophils and promote neutrophil survival in infected lungs, which resulted in an abundance of neutrophils (61). This caused the NLR levels in COVID-19 patients to increase, reflecting the negative immune system activation that forms a part of the illness.

Regarding the abnormality of blood cell count, Sambataro et al. previously noted that patients with COVID-19 had a substantial decrease in WBC count at admission and a higher reduced neutrophil count relative to lymphocyte count in

comparison to non-COVID-19 community-acquired pneumonia patients (62). The clinical consequence is that a convenient and simple method for early COVID-19 diagnostic triage might be the WBC count.

NLR in COVID-19 studies

In COVID-19, NLR is the biomarker that has been researched the most. (Table 2) lists the results of these investigations (63–87). Several investigations substantially confirmed NLR's predictive value for the development of severe illness and mortality (88–90).

In an observational, retrospective, and multicentric evaluation of critical patients with COVID-19 infection in an intensive care unit, non-survivors showed substantially lower lymphocyte levels (p: 0.003), greater NLR (p: 0.001), and greater derived NLR levels (p: 0.002) (91). Additionally, NLR and derived NLR had the strongest independent predictive values for mortality and the requirement for invasive mechanical ventilation (91). Another study of 411 patients with COVID-19 infection demonstrated that in-hospital mortality is predicted by an NLR> 11.38 (p< 0.0001, AUC: 0.771, specificity: 65.9%, sensitivity: 77.5%) (92).

According to two comprehensive meta-analyses, on-admission NLR levels were greater in severe and non-survivor COVID-19 patients compared to non-severe and survivor patients (93,94). Despite the various NLR cut-off levels, the pooled risk ratio for mortality in patients with increased NLR values in comparison with normal NLR values was 2.74 (95% CI: 0.98-7.66) (94). The area under the curve for mortality at NLR cut-off ≥ 6.5 is 0.90, whereas the area under the curve for disease severity at NLR cut-off ≥ 4.5 is 0.85 (93). Therefore, NLR examination may enable earlier detection of severe cases, which may lower the COVID-19 infection's overall mortality.

NLR has also been suggested as a compass to predict corticosteroid medication efficacy in a large cohort research involving 12,862 patients with COVID-19 (95). Particularly, in patients who received corticosteroid treatment, admission NLR levels > 6.11 were associated with more severe disease and a decrease in 60-day death rate. Conversely, admission NLR levels ≤ 6.11 were associated with mild-to-moderate illness that did not respond to corticosteroid treatment (95).

Conclusion:

NLR is a low-cost and simple-to-obtain biomarker that reflects the balance among two immune process components: adaptive immunity, and acute and chronic inflammation. NLR can be used as a quick and affordable way to identify COVID-19 patients at increased risk of severe illness and mortality since it is simple to calculate at the bedside. It can be employed alone or in combination with other biomarkers to screen for COVID-19, make an early diagnosis or detection of it, and determine its prognosis. However, additional investigations may also be beneficial in determining the range of normalcy, adjusted for age groups.

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Conflicts of interests

No conflict of interest was observed during this study.

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Table & Figure:

Table 1. The four phases of COVID-19 infection based on the clinical severity.

Clinical severity	Symptoms	Signs and imaging
Mild	Fever, cough, myalgia, fatigue	SpO2: 95–98 % No pneumonia on imaging
Moderate	Fever, cough, fatigue	SpO2: 93–95 % Respiratory rate >24 breath/min Lobar, unilateral pneumonia on imaging
Severe	Fever, cough, dyspnea, tachypnea	SpO2< 93 % Hypoxemic acute respiratory failure Respiratory rate >30 breath/min 50% bilateral pneumonia on CT scan
Critical	Severe hypoxemia, severe dyspnea and tachypnea	Acute respiratory distress syndrome Mechanical ventilation Oxygenation index <200 mmHg Shock Multiorgan dysfunction syndrome More than 75% bilateral pneumonia on CT scan

Table 2. Characteristics of studies on the NLR in COVID-19.

Study	Country	Year	Number of patients	Study design	Outcome
Luo et al.	China	2020	298	Retrospective	Patients with critical or severe COVID-19 infection tended to have higher NLR.
Li et al.	China	2020	93	Retrospective	Chest CT scores, which had a positive correlation with the NLR, were associated with a monotonous increase in COVID-19 mortality rate.
Tatum et al.	USA	2020	125	Prospective	NLR is an independent predictor of mortality risk in patients with COVID-19 and a predictive factor for endotracheal intubation following hospitalization.
Ok et al.	Turkey	2020	139	Retrospective	Since NLR could be related to the severity of COVID-19 infection, regular use of NLR can assist in the evaluation of the disease.
Peng et al.	China	2020	220	Retrospective	Severe patients had substantially higher neutrophil percentages and NLR levels in comparison to non-severe patients.
Archana et al.	India	2021	302	Cross-sectional	In terms of predicting mortality in patients with COVID-19 infection, NLR exhibited a sensitivity of 85% and a specificity of 51%.

Prasetya et al.	Indonesia	2021	391	Retrospective	In COVID-19 patients, NLR ≥ 6 upon hospital admission may be a reliable indicator of poor outcomes.
Lopez-Escobar et al.	Spain	2021	1955	Retrospective	NLR is helpful for predicting risk of in-hospital mortality owing to COVID-19 infection.
Baqi et al.	Pakistan	2021	299	Retrospective	The deceased COVID-19 patients had greater levels of NLR, LDH, and CRP.
Asghar et al.	Pakistan	2020	191	Retrospective	Elevated NLR is strongly connected with COVID-19 patients' mortality and morbidity.
Ruiz et al.	Spain	2020	119	Retrospective	Patients with COVID-19 who had an elevated NLR at admission had a poor prognosis.
Ghazanfari et al.	Iran	2021	79	Retrospective	NLR demonstrated a substantial correlation with COVID-19 patient mortality.
Zhi-Yong Zeng et al.	China	2021	352	Prospective	NLR upon admission could be utilized as a predictor of mortality and disease severity in patients with COVID-19.
Asan et al.	Turkey	2021	695	Retrospective	The severity of COVID-19 infection was correlated with initial NLR.
Tahtasakal et al.	Turkey	2021	534	Retrospective	A higher baseline NLR, LDH, troponin, and CRP are correlated with greater disease severity.
Sepulchre et al.	Belgium	2020	198	Retrospective	The risk of in-hospital mortality was greater in COVID-19 patients with elevated NLR.
Mousavi-Nasab et al.	Iran	2020	70	Retrospective	CRP and NLR are potential early indicators for evaluating the severity and prognosis of patients with COVID-19.
Xia et al.	China	2020	63	Retrospective	NLR might serve as an early warning indicator when COVID-19 is severe.
Wang P et al.	China	2020	441	Retrospective	D-dimer and NLR assist to predict disease severity in patients with COVID-19 infection.
Ma et al.	China	2020	149	Retrospective	NLR ≥ 2.22 might be used as a predictive indication for COVID-19's early recognition and to expedite timely detection.
Xu et al.	China	2020	338	Retrospective	NLR emerges as an independent predictor for progression of disease in patients with COVID-19.
Cervantes et al.	Israel	2021	337	Cross-sectional	In severe COVID-19, the probability of mortality increased with NLR ≥ 8.5.

Ding et al.	China	2020	72	Retrospective	The length of hospitalization was shown to be positively linked with NLR from day 5 following admission.
Kong et al.	China	2020	210	Retrospective	NLR was found to be a predisposing factor for severe COVID-19 disease.
Liao et al.	China	2020	380	Retrospective	The NLR, prothrombin time, D-dimer, platelet count may present a convenient and reliable method for categorizing and predicting the severity and prognosis of COVID-19 patients.