

## Narrative review

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

Danial Soltani<sup>1</sup>, Amirhossein Mohammadzadeh<sup>2</sup>, Asef Younesi<sup>3</sup>, Nikoo Saeedi<sup>4</sup>, Nastaran Khoshhal<sup>5</sup>, Niloofar Nikpasand<sup>6</sup>, Zahra Mousavi<sup>7</sup>, Gelayol Bavafa<sup>8</sup>, Sara Naghizadeh Kashani<sup>9</sup>, Sajjad Kasraeifar<sup>10</sup>, Behnaz Hatami<sup>11\*</sup>

1. Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Orcid: 0000-0002-9721-3162
2. Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Orcid: 0000-0003-3414-8241
3. Student Research Committee, Faculty of Medicine, Bojnourd University of Medical Sciences, Bojnourd, Iran. Orcid: 0000-0002-9935-3011
4. Student Research Committee, Islamic Azad University, Mashhad Branch, Mashhad, Iran. Orcid: 0000-0003-1309-4408
5. Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Orcid: 0000-0002-1522-3974
6. Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Orcid: 0000-0002-3366-3391
7. Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Orcid: 0000-0002-2488-7828
8. Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Orcid: 0000-0002-3098-9599
9. Medical Doctor, Research Assistant, Thomas Jefferson University, Philadelphia, USA. Orcid: 0009-0006-0533-1169
10. Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Orcid: 0000-0002-5873-749X
11. Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Orcid: 0000-0002-5107-0856

**\*Corresponding authors:** Behnaz Hatami, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. **Email:** be.hatami@gmail.com

**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

Submitted: 14 Oct 2023, Revised: 2 Nov 2023, Accepted: 7 Nov 2023

## 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  $\beta$ -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 cortisol 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 discriminate 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 ( $\text{NLR} > 6.2$ ) and viral infection ( $\text{NLR} < 6$ ) (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  $\text{TNF-}\alpha^+$  NK,  $\text{IL-2}^+$  NK,  $\text{IFN-}\gamma^+$  NK, and  $\text{CD107a}^+$  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  $\text{IL-2}^+\text{CD8}^+$ ,  $\text{IFN-}\gamma^+\text{CD8}^+$ , and  $\text{CD107a}^+\text{CD8}^+$  T cells and the mean fluorescence intensity of granzyme B+CD8+ T cells than healthy subjects (60). In addition, the  $\text{IFN-}\gamma$  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  $\text{NLR} > 11.38$  ( $p < 0.0001$ , 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  $\geq 6.5$  is 0.90, whereas the area under the curve for disease severity at NLR cut-off  $\geq 4.5$  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  $\leq 6.11$  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.

### **Acknowledgments**

None

### **Funding**

None

### **Conflicts of interests**

No conflict of interest was observed during this study.

### **Ethical considerations:**

None

### **Author contribution:**

All authors met the four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors

### **References:**

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;
2. World Health Organization (2020). WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. 2020.
3. Ghodsi A, Azarfar A, Ghahremani S. A Review of Coronavirus Disease (COVID-

- 19) in Children. *J Pediatr Nephrol.* 2020;8(3).
4. Tabaraii, R., Mehrpour, S., Safdari, H., Shakeri, M., & Bahadorzadeh, M. Establishment of a Longitudinal Registry of COVID-19 ICU Patients in Qom City, Iran: Retrospective Chart Review and Analysis of Laboratory Data. *Updates in Emergency Medicine.* 2023; 2(2): 1-7.
5. Paules CI, Marston HD, Fauci AS. Coronavirus infections—more than just the common cold. *Jama.* 2020;323(8):707–8.
6. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The lancet.* 2020;395(10224):565–74.
7. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. *J Med Virol.* 2020;92(6):568–76.
8. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Travel Med.* 2020;
9. Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. *Jama.* 2020;323(14):1406–7.
10. Van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med.* 2020;382(16):1564–7.
11. Abiri, S., Ghanaatpisheh, A., Sohrabpour, M., Sanie Jahromi, M. S., Habibzadeh, S. R., Shahi, B., Foroughian, M., Maleki, F., Hakemi, A., Rayat Dost, E., & Kazeminezhad, A. Worldwide One-Year Dynamics of COVID-19 Manifestations: A Systematic Review and Meta-Analysis. *Updates in Emergency Medicine.* 2022; 2(1), 23–33.
12. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The lancet.* 2020;395(10223):507–13.
13. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun.* 2020;109:102433.
14. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak—an update on the status. *Mil Med Res.* 2020;7(1):1–10.
15. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The lancet.* 2020;395(10229):1054–62.
16. Poston JT, Patel BK, Davis AM. Management of critically ill adults with COVID-19. *Jama.* 2020;323(18):1839–41.
17. Ghodsi A, Malek A, Ghahremani S. A review of multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. *cal.* 2020;12:13.
18. Ghodsi A, Mahmoudabadi E, Ghahremani S, Malek A. Cardiac manifestations of multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 infection. *Arch Pediatr Infect Dis.* 2021;16.
19. Ghodsi A, Sarabi M, Malek A, Khakshour A. Current Treatment Guidelines of SARS-CoV-2 Related Multisystem Inflammatory Syndrome in Children: A Literature Review and Expert Opinion. *J Child Sci.* 2021;11(01):e133–40.
20. Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, Arastehfar A, Gangneux

- JP, et al. The emergence of COVID-19 associated mucormycosis: a review of cases from 18 countries. *Lancet Microbe* [Internet]. 2022 [cited 2023 Nov 7]; Available from: [https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247\(21\)00237-8/fulltext](https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00237-8/fulltext)
21. Dolatabadi S, Bakhshae M, Hosseinpour M, Noghani AA, Afzalzadeh M, Roshanzamir I, et al. Mortality and Morbidity among COVID-19-Associated Mucormycosis Patients in Iran: A Prospective Cohort Study. *Adv Infect Dis*. 2023;13(3):407–23.
  22. Akbari A, Fathabadi A, Razmi M, Zarifian A, Amiri M, Ghodsi A, et al. Characteristics, risk factors, and outcomes associated with readmission in COVID-19 patients: A systematic review and meta-analysis. *Am J Emerg Med*. 2021;
  23. Song CY, Xu J, He JQ, Lu YQ. COVID-19 early warning score: a multi-parameter screening tool to identify highly suspected patients. *MedRxiv*. 2020;
  24. Ghodsi A, Bijari M, Alamdaran SA, Saberi A, Mahmoudabadi E, Balali MR, et al. Chest computed tomography findings of COVID-19 in children younger than 1 year: a systematic review. *World J Pediatr*. 2021;1–8.
  25. Athari, M. J., Abbasi, A. R., Rafeai, E., Sarikhani, Y., & Haghbeen, M. CT scan Findings and Progressions of COVID-19 Patients in Jahrom, South of Iran. *Updates in Emergency Medicine*. 2022; 2(1), 51–59.
  26. Ciaccio M, Agnello L. Biochemical biomarkers alterations in Coronavirus Disease 2019 (COVID-19). *Diagnosis*. 2020;7(4):365–72.
  27. Henry BM, De Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med CCLM*. 2020;58(7):1021–8.
  28. Ponti G, Maccaferri M, Ruini C. Biomarkers associated with COVID-19 disease progression *Crit Rev Clin Lab Sci* 1-11. 2020.
  29. Xia X ying, Wu J, Liu H lei, Xia H, Jia B, Huang W xiang. Epidemiological and initial clinical characteristics of patients with family aggregation of COVID-19. *J Clin Virol*. 2020;127:104360.
  30. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis*. 2020;71(15):762–8.
  31. Alkhatip AAAMM, Kamel MG, Hamza MK, Farag EM, Yassin HM, Elayashy M, et al. The diagnostic and prognostic role of neutrophil-to-lymphocyte ratio in COVID-19: a systematic review and meta-analysis. *Expert Rev Mol Diagn*. 2021;21(5):505–14.
  32. Song M, Graubard BI, Rabkin CS, Engels EA. Neutrophil-to-lymphocyte ratio and mortality in the United States general population. *Sci Rep*. 2021;11(1):1–9.
  33. Buonacera A, Stancanelli B, Colaci M, Malatino L. Neutrophil to Lymphocyte Ratio: An Emerging Marker of the Relationships between the Immune System and Diseases. *Int J Mol Sci*. 2022;23(7):3636.
  34. Mortaz E, Alipoor SD, Adcock IM, Mumby S, Koenderman L. Update on neutrophil function in severe inflammation. *Front Immunol*. 2018;9:2171.
  35. Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. *Bratisl Lek Listy*. 2001;102(1):5–14.
  36. Zahorec R. Neutrophil-to-lymphocyte ratio. Sixteen-year-long history since publication of our article in Bratislava Medical Journal. *Bratisl Lek Listy*.

- 2017;118(6):321–3.
37. Zahorec R, Hulin I, Zahorec P. Rationale Use of Neutrophil-to-lymphocyte ratio for early diagnosis and stratification of COVID-19. *Bratisl Lek Listy*. 2020;121(7):466–70.
  38. Rahmanian, M., & Rahmanian, Z. Pulse Therapy with Corticosteroids in Covid-19 Pneumonia: A Case Report. *Updates in Emergency Medicine*. 2022; 2(1), 67–70
  39. Reiske L, Schmucker S, Pfaffinger B, Weiler U, Steuber J, Stefanski V. Intravenous infusion of cortisol, adrenaline, or noradrenaline alters porcine immune cell numbers and promotes innate over adaptive immune functionality. *J Immunol*. 2020;204(12):3205–16.
  40. Hai L, Hu ZD. The clinical utility of neutrophil to lymphocyte ratio in pregnancy related complications: a mini-review. *J Lab Precis Med*. 2020;5(1):1–9.
  41. Agnello L, Bivona G, Vidali M, Scazzone C, Giglio RV, Iacolino G, et al. Monocyte distribution width (MDW) as a screening tool for sepsis in the Emergency Department. *Clin Chem Lab Med CCLM*. 2020;58(11):1951–7.
  42. Bhat T, Teli S, Rijal J, Bhat H, Raza M, Khoueiry G, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. *Expert Rev Cardiovasc Ther*. 2013;11(1):55–9.
  43. Haybar H, Pezeshki SMS, Saki N. Evaluation of complete blood count parameters in cardiovascular diseases: an early indicator of prognosis? *Exp Mol Pathol*. 2019;110:104267.
  44. Huang Z, Fu Z, Huang W, Huang K. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: a meta-analysis. *Am J Emerg Med*. 2020;38(3):641–7.
  45. Takada T, Hoogland J, Yano T, Fujii K, Fujiishi R, Miyashita J, et al. Added value of inflammatory markers to vital signs to predict mortality in patients suspected of severe infection. *Am J Emerg Med*. 2020;38(7):1389–95.
  46. Chen J liang, Wu J nan, Lv X dong, Yang Q chang, Chen J rong, Zhang D mei. The value of red blood cell distribution width, neutrophil-to-lymphocyte ratio, and hemoglobin-to-red blood cell distribution width ratio in the progression of non-small cell lung cancer. *PLoS One*. 2020;15(8):e0237947.
  47. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. *J Med Virol*. 2020;
  48. Ghodsi A, Mirimoghaddam MM, Sarabi M, Dehghan Tarazjani A, Omranzadeh A, Mahdavi Rashed M, et al. Neutrophil-to-lymphocyte ratio as a novel and valuable marker for assessing disease severity in Ulcerative colitis, Multiple sclerosis, and Kawasaki disease: A review. *J Basic Res Med Sci*. 2020;7(3):62–70.
  49. Omranzadeh A, Baradaran A, Ghodsi A, Arekhi S, Dadgarmoghaddam M, Mirshekaran A, et al. Neutrophil-to-Lymphocyte Ratio as an Inflammatory Marker in Familial Mediterranean Fever: A Systematic Review and Meta-analysis. *J Child Sci*. 2021;11(01):e100–9.
  50. Khorrampazhouh N, Omranzadeh A, Fazeli B, Zarifian A, Ghodsi A, Amir Khanlou F, et al. A Systematic Review and Meta-analysis of Clinical Studies on Ankylosing Spondylitis and Neutrophil to Lymphocyte Ratio. *Curr Rheumatol Rev*. 2021;
  51. Han Q, Wen X, Wang L, Han X, Shen Y, Cao J, et al. Role of hematological parameters in the diagnosis of influenza virus infection in patients with respiratory tract infection symptoms. *J Clin Lab Anal*. 2020;34(5):e23191.
  52. Tajiri K, Baba H, Kawai K, Minemura M, Yasumura S, Takahara T, et al.

- Neutrophil-to-lymphocyte ratio predicts recurrence after radiofrequency ablation in hepatitis B virus infection. *J Gastroenterol Hepatol.* 2016;31(7):1291–9.
53. Azab B, Camacho-Rivera M, Taioli E. Average values and racial differences of neutrophil lymphocyte ratio among a nationally representative sample of United States subjects. *PloS One.* 2014;9(11):e112361.
54. Holub M, Beran O, Kaspříková N, Chalupa P. Neutrophil to lymphocyte count ratio as a biomarker of bacterial infections. *Open Med.* 2012;7(2):258–61.
55. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? *BMC Res Notes.* 2017;10(1):1–4.
56. Fest J, Ruitter R, Ikram MA, Voortman T, van Eijck CH, Stricker BH. Reference values for white blood-cell-based inflammatory markers in the Rotterdam Study: a population-based prospective cohort study. *Sci Rep.* 2018;8(1):1–7.
57. Karakonstantis S, Kalemaki D, Tzagkarakis E, Lydakakis C. Pitfalls in studies of eosinopenia and neutrophil-to-lymphocyte count ratio. *Infect Dis.* 2018;50(3):163–74.
58. Naess A, Nilssen SS, Mo R, Eide GE, Sjursen H. Role of neutrophil to lymphocyte and monocyte to lymphocyte ratios in the diagnosis of bacterial infection in patients with fever. *Infection.* 2017;45(3):299–307.
59. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct Target Ther.* 2020;5(1):1–3.
60. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol.* 2020;17(5):533–5.
61. Antonioli L, Fornai M, Pellegrini C, Blandizzi C. NKG2A and COVID-19: another brick in the wall. *Cell Mol Immunol.* 2020;17(6):672–4.
62. Sambataro G, Giuffrè M, Sambataro D, Palermo A, Vignigni G, Cesareo R, et al. The Model for Early COVID-19 Recognition (MECOR) score: A proof-of-concept for a simple and low-cost tool to recognize a possible viral etiology in community-acquired pneumonia patients during COVID-19 outbreak. *Diagnostics.* 2020;10(9):619.
63. Luo X, Zhou W, Yan X, Guo T, Wang B, Xia H, et al. Prognostic value of C-reactive protein in patients with coronavirus 2019. *Clin Infect Dis.* 2020;71(16):2174–9.
64. Li L, Yang L, Gui S, Pan F, Ye T, Liang B, et al. Association of clinical and radiographic findings with the outcomes of 93 patients with COVID-19 in Wuhan, China. *Theranostics.* 2020;10(14):6113.
65. Tatum D, Taghavi S, Houghton A, Stover J, Toraih E, Duchesne J. Neutrophil-to-lymphocyte ratio and outcomes in Louisiana COVID-19 patients. *Shock Augusta Ga.* 2020;
66. Ok F, Erdogan O, Durmus E, Carkci S, Canik A. Predictive values of blood urea nitrogen/creatinine ratio and other routine blood parameters on disease severity and survival of COVID-19 patients. *J Med Virol.* 2021;93(2):786–93.
67. Peng F, Lei S, Wu C, Yu B, Zhong Y, Wu S. Neutrophil percentage and neutrophil-to-monocyte ratio as independent risk factors in the severity of COVID-19. 2020;
68. Archana B, Shyamsunder S, Das R. Validity of markers and indexes of systemic inflammation in predicting mortality in COVID 19 infection: a hospital based cross sectional study. *medRxiv.* 2021;
69. Prasetya IB, Lorens JO, Sungono V, El-Khobar KE, Wijaya RS. Prognostic value of

- inflammatory markers in patients with COVID-19 in Indonesia. *Clin Epidemiol Glob Health*. 2021;11:100803.
70. López-Escobar A, Madurga R, Castellano JM, Velázquez S, Suárez del Villar R, Menéndez J, et al. Risk score for predicting in-hospital mortality in COVID-19 (rim score). *Diagnostics*. 2021;11(4):596.
71. Baqi S, Naz A, Sayeed MA, Khan S, Ismail H, Kumar V, et al. Clinical characteristics and outcome of patients with severe COVID-19 pneumonia at a public sector hospital in Karachi, Pakistan. *Cureus*. 2021;13(2).
72. Asghar MS, Khan NA, Haider Kazmi SJ, Ahmed A, Hassan M, Jawed R, et al. Hematological parameters predicting severity and mortality in COVID-19 patients of Pakistan: a retrospective comparative analysis. *J Community Hosp Intern Med Perspect*. 2020;10(6):514–20.
73. Jimeno S, Ventura PS, Castellano JM, García-Adasme SI, Miranda M, Touza P, et al. Prognostic implications of neutrophil-lymphocyte ratio in COVID-19. *Eur J Clin Invest*. 2021;51(1):e13404.
74. Ghazanfari T, Salehi MR, Namaki S, Arabkheradmand J, Rostamian A, Chenary MR, et al. Interpretation of hematological, biochemical, and immunological findings of COVID-19 disease: biomarkers associated with severity and mortality. *Iran J Allergy Asthma Immunol*. 2021;20(1):46–66.
75. Zeng ZY, Feng SD, Chen GP, Wu JN. Predictive value of the neutrophil to lymphocyte ratio for disease deterioration and serious adverse outcomes in patients with COVID-19: a prospective cohort study. *BMC Infect Dis*. 2021;21(1):1–6.
76. Asan A, Üstündağ Y, Koca Ni, Şimşek A, Sayan HE, Parildar Hü, et al. Do initial hematologic indices predict the severity of COVID-19 patients? *Turk J Med Sci*. 2021;51(1):39–44.
77. Tahtasakal CA, Oncul A, Sevgi DY, Celik E, Ocal M, Turkkan HM, et al. Could we predict the prognosis of the COVID-19 disease? *J Med Virol*. 2021;93(4):2420–30.
78. Sepulchre E, Pittie G, Stojkovic V, Haesbroek G, Crama Y, Schyns M, et al. Covid-19: contribution of clinical characteristics and laboratory features for early detection of patients with high risk of severe evolution. *Acta Clin Belg*. 2022;77(2):261–7.
79. Mousavi-Nasab SD, Mardani R, Azadani HN, Vasmehjani AA, Sabeti S, Darazam IA, et al. Neutrophil to lymphocyte ratio and C-reactive protein level as prognostic markers in mild versus severe COVID-19 patients. *Gastroenterol Hepatol Bed Bench*. 2020;13(4):361.
80. Xia X, Wen M, Zhan S, He J, Chen W. An increased neutrophil/lymphocyte ratio is an early warning signal of severe COVID-19. *Nan Fang Yi Ke Da Xue Xue Bao*. 2020;40(3):333–6.
81. Wang P, Sha J, Meng M, Wang C, Yao Q, Zhang Z, et al. Risk factors for severe COVID-19 in middle-aged patients without comorbidities: a multicentre retrospective study. *J Transl Med*. 2020;18(1):1–12.
82. Ma Y, Shi N, Fan Y, Wang J, Zhao C, Li G, et al. Predictive value of the neutrophil-to-lymphocyte ratio (NLR) for diagnosis and worse clinical course of the COVID-19: findings from ten provinces in China. 2020;
83. Xu J, Hu S, Li S, Wang W, Wu Y, Su Z, et al. A composite index predicts disease progression in early stages of COVID-19: a propensity score-matched cohort study. 2020;
84. Montiel-Cervantes LA, Medina G, Cruz-Domínguez P, Perez-Tapia SM, Jimenez-Martinez MC, Arrieta-Oliva HI, et al. Poor Survival in COVID-19 Associated with Lymphopenia and Higher Neutrophile-Lymphocyte Ratio. *Isr Med Assoc J IMAJ*. 2021;23(3):153–9.

85. Ding X, Yu Y, Lu B, Huo J, Chen M, Kang Y, et al. Dynamic profile and clinical implications of hematological parameters in hospitalized patients with coronavirus disease 2019. *Clin Chem Lab Med CCLM*. 2020;58(8):1365–71.
86. Kong M, Zhang H, Cao X, Mao X, Lu Z. Higher level of neutrophil-to-lymphocyte is associated with severe COVID-19. *Epidemiol Infect*. 2020;148.
87. Liao D, Zhou F, Luo L, Xu M, Wang H, Xia J, et al. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. *Lancet Haematol*. 2020;7(9):e671–8.
88. Seyit M, Avci E, Nar R, Senol H, Yilmaz A, Ozen M, et al. Neutrophil to lymphocyte ratio, lymphocyte to monocyte ratio and platelet to lymphocyte ratio to predict the severity of COVID-19. *Am J Emerg Med*. 2021;40:110–4.
89. Fois AG, Paliogiannis P, Scano V, Cau S, Babudieri S, Perra R, et al. The systemic inflammation index on admission predicts in-hospital mortality in COVID-19 patients. *Molecules*. 2020;25(23):5725.
90. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern Med*. 2020;180(10):1345–55.
91. Moisa E, Corneci D, Negoita S, Filimon CR, Serbu A, Negutu MI, et al. Dynamic changes of the neutrophil-to-lymphocyte ratio, systemic inflammation index, and derived neutrophil-to-lymphocyte ratio independently predict invasive mechanical ventilation need and death in critically ill COVID-19 patients. *Biomedicines*. 2021;9(11):1656.
92. Regolo M, Vaccaro M, Sorce A, Stancanelli B, Colaci M, Natoli G, et al. Neutrophil-to-Lymphocyte ratio (NLR) is a promising predictor of mortality and admission to intensive care unit of COVID-19 patients. *J Clin Med*. 2022;11(8):2235.
93. Li X, Liu C, Mao Z, Xiao M, Wang L, Qi S, et al. Predictive values of neutrophil-to-lymphocyte ratio on disease severity and mortality in COVID-19 patients: a systematic review and meta-analysis. *Crit Care*. 2020;24(1):1–10.
94. Simadibrata DM, Calvin J, Wijaya AD, Ibrahim NAA. Neutrophil-to-lymphocyte ratio on admission to predict the severity and mortality of COVID-19 patients: A meta-analysis. *Am J Emerg Med*. 2021;42:60–9.
95. Cai J, Li H, Zhang C, Chen Z, Liu H, Lei F, et al. The neutrophil-to-lymphocyte ratio determines clinical efficacy of corticosteroid therapy in patients with COVID-19. *Cell Metab*. 2021;33(2):258–69.

**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	SpO <sub>2</sub> : 95–98 % No pneumonia on imaging
Moderate	Fever, cough, fatigue	SpO <sub>2</sub> : 93–95 % Respiratory rate >24 breath/min Lobar, unilateral pneumonia on imaging
Severe	Fever, cough, dyspnea, tachypnea	SpO <sub>2</sub> < 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, $NLR \geq 6$ 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	$NLR \geq 2.22$ 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 $NLR \geq 8.5$ .

---

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.