

Review Article:

Neutrophils to Lymphocytes Ratio and the Prognosis of the COVID-19 Patients



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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a new pandemic virus, a global concern, and has threatened human health. This virus binds to the Angiotensin-Converting Enzyme 2 (ACE2) that is expressed on different cells, especially on the alveolar cells. So the virus can enter the lung cells and causes respiratory syndromes. In Coronavirus Disease 2019 (COVID-19) that is caused by SARS-CoV-2, respiratory failure, and acute inflammation is the main cause of death. According to several reports, multiple factors, such as Neutrophils to Lymphocytes Ratio (NLR) have prognostic potentials in COVID-19. This study aims to review this parameter to have a better prediction about the condition of the patients and their treatments. According to this review, the NLR ratio that is related to the innate immune responses and inflammation can be helpful in the discrimination of severe from non-severe cases of COVID-19 patients.

Introduction

The Coronaviridae family has three main members of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), middle east respiratory syndrome coronavirus (MERS-CoV), and Severe Acute

Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). All these members with single-stranded RNA can cause several disorders, especially respiratory ones [1, 2]. Among them, the SARS-CoV-2 is a new virus that has threatened human health and is a global concern [3].

This deadly virus has several structural proteins such as protein Spike (S), Envelope (E), Nucleocapsid (N), and

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Membrane (M). This RNA virus binds to the angiotensin-converting enzymes 2 (ACE2) using its S protein. The ACE2 receptor is expressed on different cells, especially on the alveolar cells. So the virus can enter the lung cells and causes respiratory syndromes [4, 5]. During this syndrome, high levels of pro-inflammatory cytokines, including interleukin-6 (IL-6) are secreted by immune cells contributing to the inflammatory responses [6, 7]. So, in coronavirus disease 2019 (COVID-19) respiratory failure and acute inflammation are the main causes of death [8].

According to several reports, multiple factors have prognostic potentials in COVID-19, such as serum amyloid A, procalcitonin, C-reactive Protein (CRP), and Neutrophils/Lymphocytes Ratio (NLR) [9, 10]. This study aims to review the NLR, as a parameter involved in the diagnosis of respiratory inflammation, and provides a better prediction about the condition of the patients and their treatments.

Immunopathogenesis of SARS-CoV-2

SARS-CoV-2 binds to its receptor on the host cells and enters them. Like SARS-CoV, SARS-CoV-2 uses ACE2 for infecting the cells. This receptor is mainly expressed on epithelial cells, alveolar epithelial cells, vascular endothelial cells, and macrophages in the lung. So these cells are the main targets of SARS-CoV-2 [11-13].

After the entrance of the virus, large amounts of pro-inflammatory cytokines such as interferon-gamma (IFN- γ), IL-6, IL-12, IL-18, IL-1 β , IL-33, tumor necrosis factor-alpha (TNF- α), etc. along with several chemokines such as CXCL8 and CCL2 and some others are secreted by immune cells. So, inflammatory monocytes and other leukocytes migrate to the lungs and inflammatory responses occur [6, 7]. In many patients, it was reported that the neutrophil count increased. In this condition, in addition to the virus, the inflammatory cells can cause damage; for example by secretion of Reactive Oxygen Species (ROS) and proteases [14]. These activated cells can also cause inflammation-induced pulmonary damage leading to complications such as pneumonia, and Acute Respiratory Distress Syndrome (ARDS), which is one of the common reasons leading to death in patients infected with SARS-CoV-2 [15-17].

The viruses of the lungs can enter the blood and cause viremia. Then the virus may enter the organs expressing ACE2, such as the renal, heart, and gastrointestinal tract. These events will result in multi-organ failure (especially renal and hepatic systems) and finally death [18].

According to several reports, multiple factors determine the severity of the COVID-19, such as NLR and the levels of inflammatory cytokines [9, 10].

Immune responses in COVID-19

An efficient immune response is essential in eliminating the virus. The patients with effective immune responses can usually control and restrict the disease in the early phase, but in patients with no effective immune response, for example, older patients or those with predisposing disorders, the severity of the infection is worse. However, the immune cells sometimes can damage the host tissues and worsen the disease condition [18, 19].

Innate immunity

SARS-CoV-2 binds to ACE2 and releases its RNA into the target cells. The RNA is recognized by endosomal Toll-like Receptors (TLRs) such as TLR3, TLR7-9, and also retinoic acid-inducible gene I (RIG-I) and melanoma-differentiation-associated gene 5 (MDA5). These molecules induce the initiation of signaling pathways that resulted in the production of IFN-I and many inflammatory cytokines and chemokines [20-23]. One of the main chemokines secreted during SARS-CoV-2 infection is CXCL8 that causes inflammatory cell recruitment such as neutrophils [6, 7].

Neutrophils are among the circulating phagocytes of the innate immune system. These are the first cells recruited to the inflammatory sites. So during the infections, the number of these cells increases in the blood. They release the enzymes that are in their granules. Although these cells have effective roles in defending against microorganisms, the released enzymes resulting from their degranulation could injure the tissues of the host [24-26]. It was observed that during ARDS, the neutrophil count in infected patients increases [15]. They induce pro-inflammatory cytokine and chemokine secretion, so they could damage the lungs and cause hemorrhagic lesions. According to the studies, neutrophilia is one of the most dangerous manifestations in infected patients and causes severe infections [27].

Neutrophil Extracellular Traps (NET) formation is one of the mechanisms that neutrophils use for killing the pathogens. During the NETosis, neutrophils eject networks composed of chromatin fibers, antimicrobial peptides, and granule-derived enzymes. These structures are called NET [28, 29]. Besides, releasing large amounts of the Reactive Oxygen Species (ROS), overexpression of the cytokines, microthrombosis, Acute Lung Injury

(ALI), and ARDS are also linked to the NETosis [30-33]. Some clues in COVID-19 patients such as increased level of the free DNA, myeloperoxidase-DNA, and citrullinated histone H3 in their blood samples, showed that the NETosis following neutrophil activation can be related to the severity of the disease [34] (Figure 1).

Adaptive immunity

In addition to innate immune cells, T and B cells also have roles in defending against viral infections and eliminating them. CD4+ T cells participate in cytokine secretion. Dendritic Cells (DCs) can uptake the SARS-CoV-2 and after processing, they present the epitopes to T cells and make them produce IFN-γ. The role of cytotoxic T lymphocytes (CTLs) against viral infections is killing the infected cells. According to the research, T cells have significant roles against SARS-CoV-2 and insufficient T cell response is involved in ARDS pathogenesis [35, 36].

During COVID-19, the T cell count of the peripheral blood is decreased, and usually, lymphopenia is reported, because these cells are accumulated in the lungs for controlling the infection [37, 38]. This condition is more intense in severe cases. In previous studies, it was demonstrated that naive T helper cells increase and memory T helper cells decrease, both in patients with severe forms of the disease. Besides, the reduction of CD4+T helper cells and CD8+cytotoxic T cells in all infected individuals were also observed.

During COVID-19, lymphocyte depletion occurs [39]. It is believed that like MERS-CoV, the SARS-CoV-2

could also induce lymphocyte apoptosis. Although the exact mechanism of the lymphocyte apoptosis is unclear, some mechanisms seem to have roles in this event, such as Activation-induced Cell Death (AICD) via Fas and FasL engagement, and lymphocyte stimulation by pro-inflammatory cytokines like IL-6 [40]. Additionally, it was demonstrated that the stress response of the cells that is mediated by p53, can induce apoptosis and senescence [41]. Accumulatively, as lymphocytes have important roles in defending against SARS-CoV-2, the lymphopenia resulted from lymphocyte depletion can be associated with the severity of the disease.

B lymphocytes also have a significant function in COVID-19. They produce neutralizing antibodies, limit the viral infection, and protect against reinfection. The antibodies can reduce the virus titer in patients. Antibodies against viruses have different mechanisms: some of them are neutralizing and they are against spike and nucleocapsid proteins. They could prevent the binding of the virus to the receptor on host cells. Some others have opsonization function; they help phagocytes to eliminate the virus. They can also activate the complement proteins. According to some studies, the delayed and poor antibody response is related to severe outcomes [15, 42, 43]. Several reports have demonstrated that the severity of the COVID-19 is associated with increased antibody response (Figure 1) [43, 44].

Neutrophil lymphocyte ratio

The neutrophil count of the peripheral blood should be divided into the lymphocyte count for measuring the

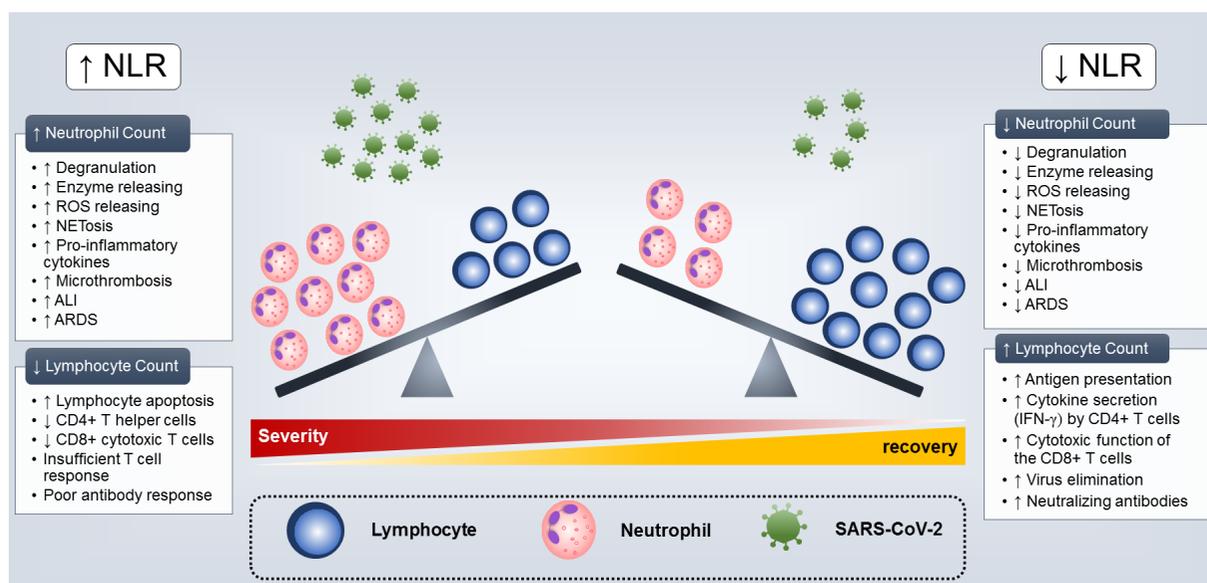


Figure 1. The correlation between NLR ratio and the severity of the COVID-19

Table 1. The summary of the studies about the use of Neutrophil to Lymphocyte Ratio (NLR) as a prognostic marker

Disease	Sample Size	Results	References
End-Stage Renal Disease (ESRD)	61 patients	Levels of NLR and tumor necrosis factor (TNF)- α were positively correlated	[45]
Gastric cancer	1028 patients	Elevated NLRs are associated with low survival and poor prognosis	[15]
Any cancer population	1498 patients	For every unit augment in NLR, the risk of cancer-associated death will be increased by about 10%	[49]
Acute respiratory distress syndrome (ARDS)	224 patients	High NLR associated with the poor outcome in critically ill patients	[43]
ARDS	275 patients	NLR in non-survivors was significantly higher than the survivors NLR more than 14, was associated with a shorter overall survival	[48]
AIV-H7N9 influenza	237 patients	NLR in the fatal group was significantly higher than those of the survival group NLR was independently associated with fatality	[55]
Respiratory infections	307 patients 100 healthy people	The influenza virus-infected group had significantly higher NLR than the control group NLR is a more sensitive inflammatory marker than other common hematological parameters	[53]
COVID-19	222 patients	The severity rate in patients with elevated NLR was higher, but the recovery rate was lower than the cases with lower NLRs In NLR high patients, the levels of inflammatory cytokines such as IL-6 and IL-2 were increased but the number of CD4+ T cells was decreased	[41]
COVID-19	344 patients	NLR is a very specific and sensitive marker in predicting the severity of patients with COVID-19 especially in patients over 50 years	[54]
COVID-19	115 patients	NLR was the most important prognostic factor for progression, followed by age The incidence of critically ill patients with NLR \geq 3.13 and aged \geq 50 years was 50%, and 9.1% in aged \geq 50 years and NLR $<$ 3.13 patients	[52]
COVID-19	452 patients	In comparison with non-severe cases of COVID-19, the severe patients have a higher neutrophil count, so the NLR tended to be higher in them	[56]
COVID-19	245 patients	The risk of mortality during hospitalization in cases with elevated NLR was higher This correlation was more significant in male patients than the female cases	[51]
COVID-19	80 patients	In COVID-19 positive patients, the NLR was significantly higher When NLR was more than 2.4, the probability of COVID-19 was 20-fold greater	[36]
COVID-19	210 patients	The severe group had higher NLRs than the mild group The highest tertile of NLR showed a 5.9-fold elevated incidence of severity relative to that of the lowest tertile	[50]
COVID-19	230 patients	Some factors are associated with the severity of the disease, such as; NLR, underlying disease (cardiovascular disease), male sex, and pulse There is a positive correlation between NLR and the levels of cytokines (IL-6, IL-10) There is a negative correlation between NLR and the proportion of CD3+ and CD8+ T lymphocyte subsets There is a positive correlation between NLR and the severity of the disease The higher NLR can lead to a longer course of the disease	[57]

NLR. This ratio shows the inflammatory status. The NLR is used as a prognostic marker in several conditions, such as cardiovascular diseases, cancer patients, acute pancreatitis, liver diseases, certain rheumatic diseases, and ARDS (Table 1). Moreover, the NLR was found to be associated with the hospital fatality in critically ill patients [14, 45-51].

A study conducted in 2011, showed that in End-stage Renal Disease (ESRD) patients, the levels of NLR and TNF- α were positively correlated. A patient with high levels of NLR had high levels of TNF- α [48]. So, NLR can help the prediction of the inflammation in these patients. Another study investigated the clinical and predictable roles of NLR in patients with gastric cancer. They concluded that elevated NLRs are usually associated with low survival and poor prognosis in patients with malignant tumors such as gastric cancer [14]. Based on a report, NLR can help the prediction of disease-specific outcomes in any cancer population. In this report, for every unit increase in NLR, the risk of cancer-associated death will increase by about 10% [52].

Many studies demonstrate a relationship between NLR and acute inflammatory diseases, such as ARDS (Table 1) [38, 43, 46, 51, 53-58]. Li et al. demonstrated the association of the high NLR with the poor outcome in critically ill patients with ARDS [46]. Besides, another study reported that the NLR in non-survivors was significantly higher than the survivors, and an NLR more than 14, was associated with shorter overall survival [51].

Previous studies demonstrate the cooperative relationship between NLR and viral infections in order to determine the severity of the infection (Table 1). Zhang et al. performed a retrospective study to assess the NLR in AIV-H7N9 infected patients. They conducted this study to determine the correlation of the differential leukocyte count with the virulence of AIV. They showed that the NLR in the fatal group was significantly higher than those of the survival group.

Besides, they mentioned that NLR was independently associated with fatality [58]. In a study conducted in 2019, multiple inflammatory parameters such as neutrophils, lymphocytes, platelets, and blood cell count indexes, particularly the NLR, were analyzed retrospectively in influenza-suspected patients. In comparison with the control group, the influenza virus-infected group had significantly higher NLR. Also, they introduced the NLR as a more sensitive inflammatory marker than other common parameters [56].

Some studies were done to investigate the prognostic potential of NLR in predicting the severity of patients with COVID-19. Recently it was reported that the severe cases of

COVID-19 tended to have higher NLRs (Table 1) [38, 43, 53-55, 57]. According to a study performed in 2020, the severity rate in patients with elevated NLR was higher, but the recovery rate was lower than the cases with lower NLRs. In patients with high NLR, the levels of inflammatory cytokines such as IL-6 and IL-2 increased but the number of CD4+ T cells decreased [43].

Another report done in 2020 divided the COVID-19 patients into 2 groups based on their age: one group of the patients under 50 years, and another group of patients with 50 or over 50 years. According to their results, NLR is a very specific and sensitive marker in predicting the severity of patients with COVID-19, especially in patients over 50 years [57].

Liu et al. analyzed the data of 115 patients with COVID-19 pneumonia and screened the independent risk factors affecting the incidence of critical illness. It was found that NLR was the most important prognostic factor for the disease prognosis, followed by age. Furthermore, according to the NLR and age stratification, the incidence of critically-ill and ≥ 50 years patients with NLR ≥ 3.13 was 50%, and with NLR < 3.13 , it was 9.1% [55]. Qin C et al. reported that in comparison with mild cases of COVID-19, the severe cases had a higher neutrophil count, so the NLR tended to be higher in them [59]. In a cohort study on 245 COVID-19 patients, it was observed that the risk of mortality during hospitalization in cases with elevated NLR was higher. This correlation was more significant in male patients than in female cases [54].

Nalbant et al. performed a cohort study on 54 COVID-19 positive and 26 COVID-19 negative individuals. In COVID-19 positive patients, the NLR was significantly higher. They found that when NLR was more than 2.4, the probability of COVID-19 was 20-fold greater [38]. Another report included 210 COVID-19 patients, and among them, 87 cases were diagnosed as severe cases. The severe group had higher NLRs than the mild group.

The highest tertile of NLR showed a 5.9-fold elevated incidence of severity relative to that of the lowest tertile [53]. In a study performed in 2020, the clinical data of 230 patients diagnosed with non-mild COVID-19 were analyzed. The researchers found some factors associated with the severity of the disease, such as NLR, underlying disease (cardiovascular disease), male sex, and pulse. They found a positive correlation between NLR and the levels of cytokines (IL-6, IL-10) and a negative correlation between NLR and the proportion of CD3+ and CD8+ T lymphocyte subsets. Also, there is a positive correlation between NLR and the severity of the disease and a higher NLR can prolong the course of the disease [60].

Conclusions

Based on different studies about NLR and the innate immune responses and inflammation, this ratio can be helpful in the discrimination of severe from non-severe patients with COVID-19 (Figure 1).

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed about the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished, and if desired, the research results would be available to them.

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Authors' contributions

Supervision and validation: Seyed Mahmoud Hashemi, Saeed Namaki; Investigation and resources: Mohammad Mahmoudi, Mahsa Taghavi-Farahabadi; Conceptualization, writing - original draft, writing – review & editing: All authors.

Conflicts of interest

The authors declare no conflict of interest.

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