

# Clinical Significance and Diagnostic Utility of NLR, LMR, PLR and SII in the Course of COVID-19: A Literature Review

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**Abstract:** Nowadays, society is increasingly struggling with infectious diseases that are characterized by severe course and even death. Recently, the whole world has faced the greatest epidemiological threat, which is COVID-19 caused by SARS CoV-2 virus. SARS CoV-2 infection is often accompanied by severe inflammation, which can lead to the development of different complications. Consequently, clinicians need easily interpreted and effective markers of inflammation that can predict the efficacy of the treatment and patient prognosis. Inflammation is associated with changes in many biochemical and hematological parameters, including leukocyte counts and their populations. In COVID-19, changes in leukocytes count populations such as neutrophils, lymphocytes or monocytes are observed. The numerous research confirm that indicators like neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelets-to-lymphocyte ratio (PLR) and systemic inflammatory index (SII) may prove effective in assessment patient prognosis and choosing optimal therapy. Therefore, in this review, we would like to summarize the latest knowledge about the diagnostic utility of systemic inflammatory ratios – NLR, LMR, PLR and SII in patients with COVID-19. We focused on the papers evaluating the diagnostic utility of inflammatory ratios using ROC curve published in the recent 3 years. Identification of biomarkers associated with inflammation would help the selection of patients with severe course of COVID-19 and high risk of death.

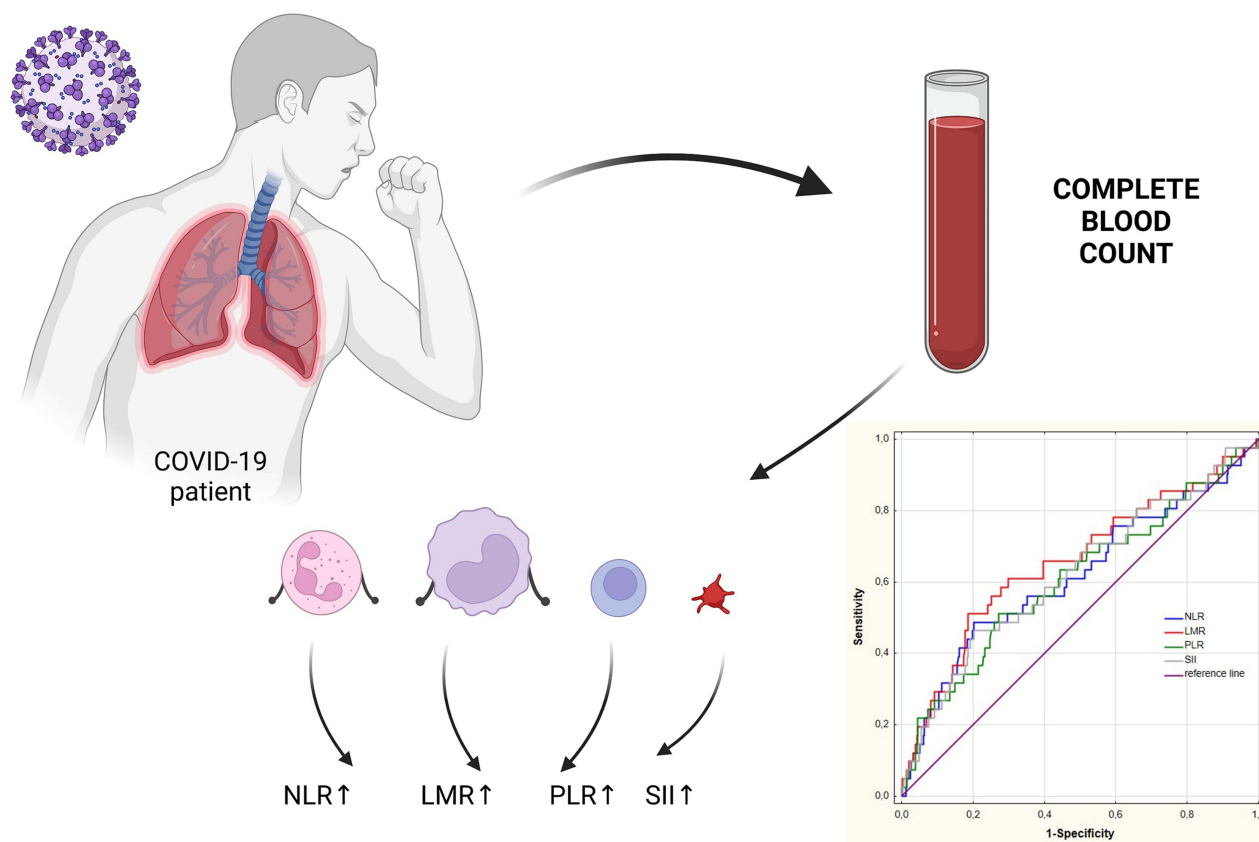
**Keywords:** COVID-19, inflammatory ratios, NLR, LMR, PLR, SII

## Introduction

Every day, the human body comes into contact with numerous pathogens that may trigger the development of various diseases. In recent years, SARS-CoV-2 virus which causes COVID-19 (coronavirus disease) has become particularly important and is now a serious health problem. The first cases of COVID-19 were reported in Wuhan, Hubei Province, China in November 2019, while in Poland the first case of the disease was confirmed on March 4, 2020.<sup>1-3</sup> The total number of COVID-19 cases dated to the beginning of July 2022 worldwide was over 562 million, of which about 6.37 million resulted in death of a patient. In Poland, there were about 6.03 million confirmed cases of COVID-19 and almost 116,000 deaths. The rapidly growing statistics on the number of infections and deaths prompted researchers to accurately classify the etiological agent, delve into the mechanism of the disease development and its complications, and search for markers, effective treatment plans and ways to prevent infection.

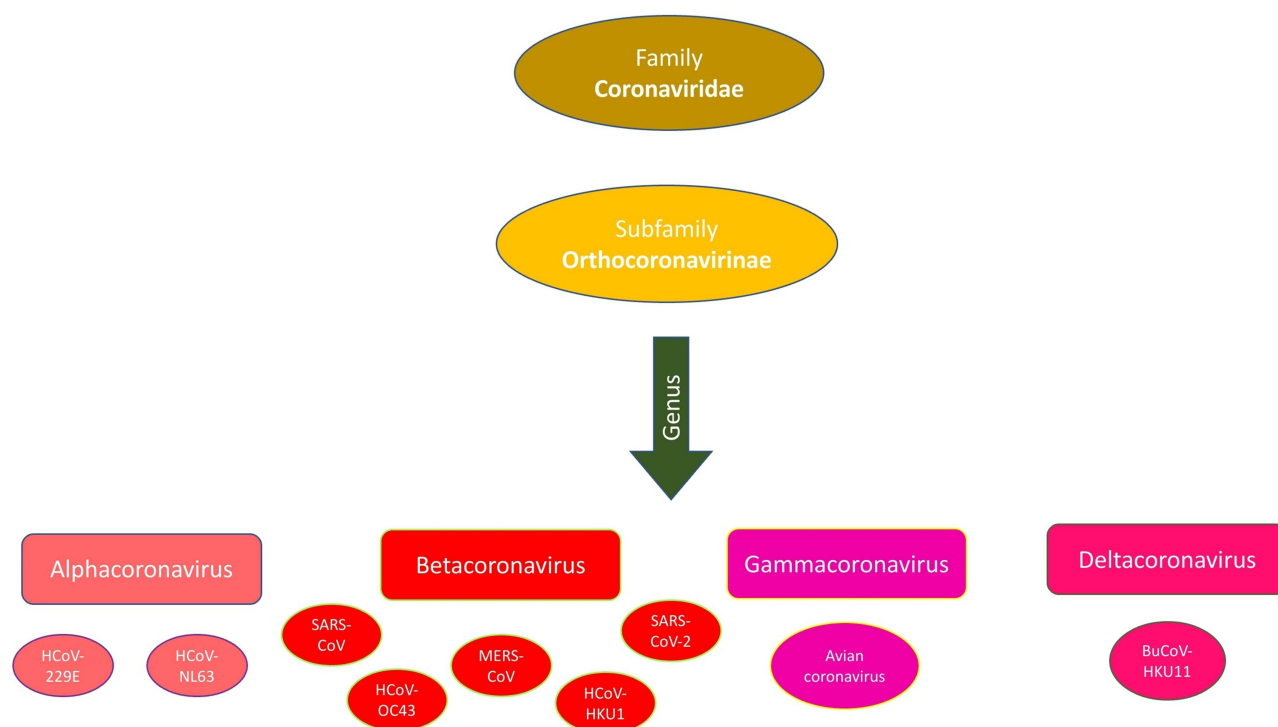
It has been discovered that SARS-CoV-2 virus is a member of the *Coronaviridae* family which also includes over 40 different species of viruses that can infect animals and humans (Figure 1).<sup>1,24</sup> The first human coronaviruses were detected in the early 1960s. Some of them, including CoV-229E, CoV-OC43, HCoV-NL63 and HCoV-HKU1, are etiological agents of common upper respiratory tract infections.<sup>4-6</sup> Other coronaviruses include SARS-CoV-1 which caused the epidemic of severe acute

## Graphical Abstract



respiratory syndrome (SARS) in the years 2002–2004,<sup>7,8</sup> and MERS-CoV which was responsible for the development of a small epidemic of Middle East respiratory syndrome (MERS) characterized by high mortality rate.<sup>4,9–11</sup> The most infectious virus belonging to the *Coronaviridae* family is SARS-CoV-2 which is responsible for the global pandemic in 2020 that caused the most severe socio-economic crisis to date.<sup>1,12–14</sup>

The course of SARS-COV-2 virus infection is characterized by high variability, depending on the patient's condition as well as individual predisposition.<sup>15</sup> According to the reports prepared by WHO-China, patients with COVID-19 most frequently develop a dry cough, fever, fatigue, and loss of taste or smell. Less common symptoms include sore throat, headache, muscle aches, and diarrhoea. Dyspnea, difficulty breathing, absent-mindedness, chest pain, or loss of speech should prompt the patient to immediately report for diagnosis and treatment, as these symptoms may be harbingers of a severe course of infection, which may ultimately lead to respiratory failure and death of the patient. Patients from risk groups, such as the elderly, the obese, people with chronic diseases, those with immunodeficiency, and those who have not been vaccinated, are particularly vulnerable.<sup>15,16</sup> It is well known that majority of symptoms are caused by inflammation which is why many scientists are conducting research and trying to discover a new specific and sensitive marker that would reflect the severity of inflammation and thus the condition of the patient. This review is the first summary of the latest knowledge on the diagnostic utility of systemic inflammatory ratios – neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelets-to-lymphocyte ratio (PLR) and Systemic Inflammatory Index (SII) and their application in monitoring of patients with COVID-19. Identification of biomarkers associated with inflammation would help the selection of patients with severe course of COVID-19 and high risk of death.



**Figure 1** Taxonomic classification of coronavirus.

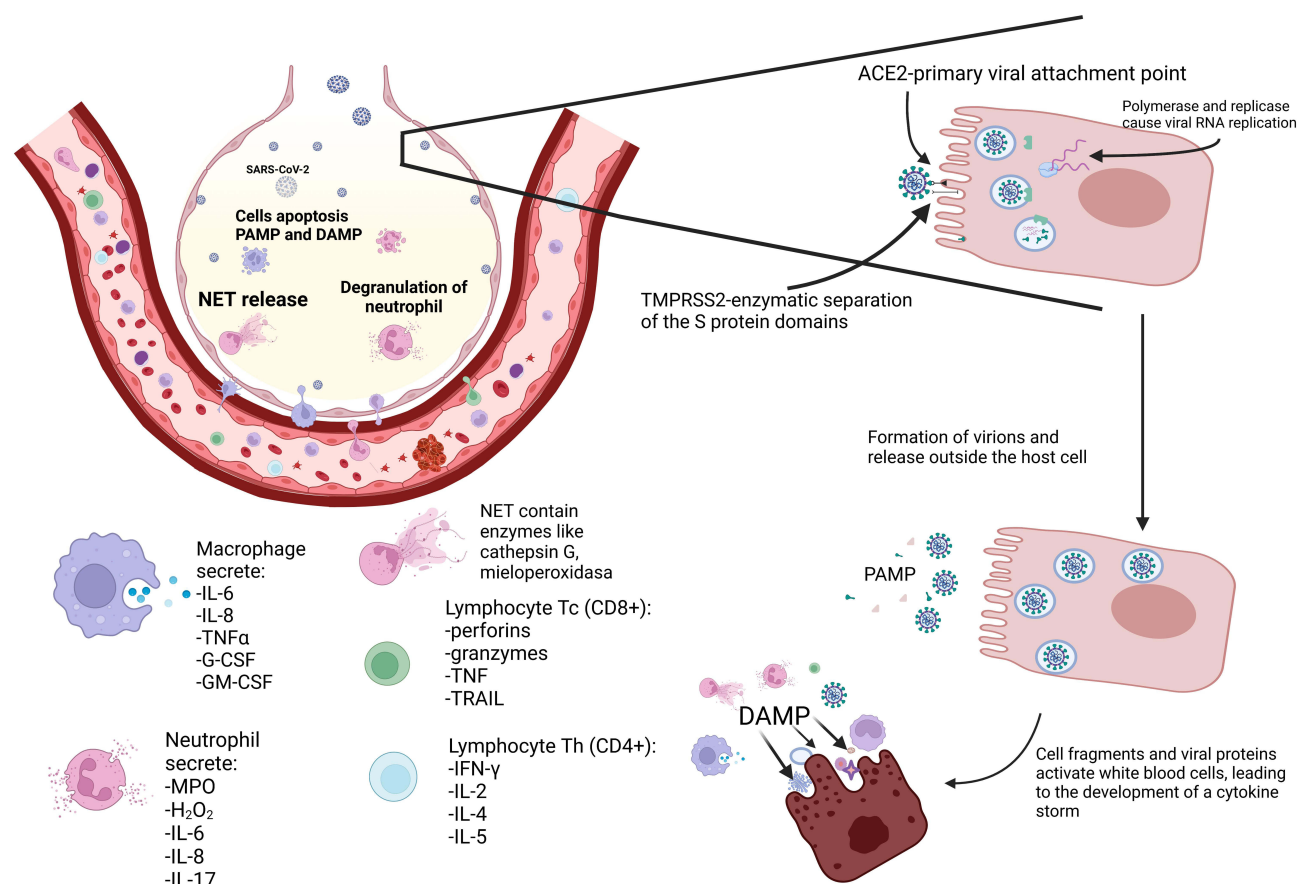
## Search Strategy

We searched PubMed database was searched for sources using the following keywords: NLR, neutrophil-to-lymphocyte ratio, PLR, lymphocyte-to-monocyte ratio, LMR, platelets-to-lymphocyte ratio, PLR, systemic inflammatory index, SII, inflammation, inflammatory markers, inflammatory ratios, COVID-19, SARS-CoV-2, diagnostic utility, ROC curve, AUC. Preference was given to the sources which were published within the past 3 years.

## SARS-CoV-2 Structure and Infection Mechanisms

SARS-CoV-2 is an enveloped betacoronavirus. The membrane (M) protein, the most abundant structural protein, is mainly responsible for the shape of the envelope. The genetic material of the virus consists of a single strand of ribonucleic acid with positive polarity located inside the protein capsid. The viral RNA chain consists of approximately 30,000 nucleotides and encodes four structural proteins: spike protein (S), envelope protein (E), membrane protein (M), and nucleocapsid (N).<sup>17–20</sup>

Once the virus has entered the body, the S1 subunit of the spike protein (S) attaches to the angiotensin-converting enzyme (ACE2) receptor that is present in the airway epithelium. The ACE2 receptor is physiologically involved in regulating the water and electrolyte balance of the cell. Another important protein is transmembrane serine protease 2 (TMPRSS2), which belongs to the group of scavenger receptors whose main function is to transfer a wide range of ligands into the cell by endocytosis (Figure 2). This protein is highly expressed in the nasal epithelium, respiratory tract and pneumocytes, and weaker expression in the intestines, which explains why SARS-CoV-2 initially localizes in these areas. In addition, TMPRSS2 protein with proteolytic functions cleaves and activates viral glycoproteins. The S2 protein is then released from the domain, facilitating the fusion of the virion with the host cell, or passage of the capsid via endocytosis into the cell. The E protein of SARS-CoV-2 virus contributes to acceleration of the process of infecting host cells. It belongs to small proteins classified as viroporins which combine with the cell membrane, forming protein-lipid pores in it, increasing the permeability of the membrane.<sup>17,18,20</sup> Further steps of infection include the opening of the endosome and the proteolytic cleavage of the capsid in the cytoplasm, which leads to the release of the viral genetic material. Nucleoprotein N is responsible for proper packing of the ribonucleic chain and the formation of the



**Figure 2** Host cell infection and cytokine storm in COVID-19.

ribonucleocapsid. Then, in a further step, the processes of replication, transcription and translation take place, enabling the formation of new virions and, through exocytosis, their export outside the host cells. During the replication of the genetic material of the virus and the translation process, the immune system may be activated.<sup>17,18,20</sup>

## Classifications of SARS-CoV-2 Variants

The process of duplication of genetic material in coronaviruses may lead to the formation of new mutations.<sup>21</sup> Due to the emergence of many different variants of SARS-CoV-2 virus characterized by varying severity of symptoms or virulence, the WHO introduced nomenclature based on the letters of the Greek alphabet to designate the key strains of the virus.<sup>22</sup> The table presents coronavirus variants (Table 1).<sup>23</sup>

## Inflammation

Inflammation is most commonly caused by infectious agents such as bacteria, viruses, fungi, as well as non-infectious agents including trauma, toxic substances, radiation, etc.<sup>24</sup> The human body defends itself against these agents through a passive and active immune responses. The passive response includes all mechanisms that are functionally active all the time, or initiated after the cells are exposed of harmful agents. These include cilia of epithelial cells that move mucus, tight intercellular junctions, and proteins dissolved in vascular and tissue fluids. Furthermore, small bioreactive molecules and various types of receptors embedded in the cell membrane that recognize molecular patterns on the surface of pathogens play an important role.<sup>25</sup> The function of the adaptive immune response is to activate degradation and removal of pathogens and toxic substances. However, this system could not function without the ability to recognise inflammatory triggers. Lymphocytes, which belong to the leukocyte population, are responsible for detecting pathogens and substances produced by them. Lymphocytes are divided into two main classes: T lymphocytes – included in the immune response

**Table 1** Coronavirus Variants.

WHO Designation	Lineage	Country of Primary Infection Occurrence	Mutations
Alpha	B.1.1.7	Great Britain	N501Y, P681H, 69–70 DEL
Beta	B.1.351, B.1.351.2, B.1.351.3	Republic of South Africa	N501Y, K417N, E484K
Gamma	P.1, P.1.1, P.1.2	Brazil	N501Y, K417T, E484K
Delta	B.1.617.2, AY.1, AY.2, AY.3	India	L452R, P681R, T478K
Omicron	B.1.1.529	Republic of South Africa	N501Y, N440K, P681H, S447N
Eta	B.1.525	Nigeria	E484K, F888L
Iota	B.1.526	USA	L5F, T95I, D253G, E484K, D614G
Kappa	B.1.617.1	India	L452R, E484Q, P681R
Lambda	C.37	Peru	G75V, T76I, Δ246-252, L452Q, F490S, D614G and T859N

cells, and B lymphocytes – responsible for the production of antibodies, associated with a humoral immune response. Protein antibodies can travel in the bloodstream as well as tissue or extracellular fluids, triggering a cellular response of granulocytes or macrophages. On the other hand, T lymphocytes, after detecting foreign agents such as viruses, can directly kill the infected cell by activating the process of apoptosis or by secreting signalling proteins for phagocytes.<sup>26,27</sup> Lymphocytes belong to the pool of cells that circulate in the bloodstream, so their number and activity may vary depending on the etiological agent or health status of the exposed person.<sup>28</sup>

## Inflammation and Inflammatory Cells in COVID-19

SARS-CoV-2 virus infection has a complex course and is characterized by, among others, hypoxemia. This is caused by inflammation that sometimes takes the form of an enhanced reaction (hyperinflammation). Consequently, patients with COVID-19 often present a considerable increase in the concentration of pro-inflammatory cytokines in the blood as well as the lung parenchyma.<sup>29,30</sup> A large group of cells is involved in this response – mainly monocytes, lymphocytes, neutrophils and, according to recent reports, platelets. These cells detect pathogens as well as damage to the respiratory epithelium through pathogen recognition receptors (PRRs).<sup>31</sup> They are located in the cell membrane and in the cytoplasm, which enables them to detect specific ligands. Substances bound (and recognised) by PRRs include viral proteins belonging to the large group of pathogen-associated molecular pattern (PAMP) compounds. They can appear in many tissues, such as the lungs and blood, where pathogens appear as a result of infection. In turn, proteins released from necrotic cells, for instance in the alveoli or airway epithelium, are classified as damage-associated molecular pattern (DAMP).<sup>31,32</sup> The binding of PRRs to their ligands, such as DAMP and PAMP, located in the interstitial lung tissue, leads to the induction of cytokines, thus promoting the state of “cytokine storm”.<sup>31</sup> This term refers to a self-activating cascade of cytokine production.<sup>32</sup> The consequence of this immune system hyperreaction in the course of COVID-19 is the sepsis-like condition observed in patients with severe COVID-19 infection. The cytokine storm involves, among others, such substances as IL-6, IL-8, TNF- $\alpha$ , IFN- $\gamma$ , IL-17.<sup>29–32</sup> On the other hand, the production and secretion of interferons: IFN- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$ , which are a major component of the body’s antiviral response, is weakened. Increased activity of cytokines and their decreased effect in the case of interferons result in a change in their ratio to each other, which is observed in a small group of COVID-19 patients who developed a critical illness (Figure 2).<sup>32</sup>



## Macrophages

There are several different classes of alveolar macrophages, including alveolar macrophages, influx monocytic macrophages, transitional macrophages, and monocytes. These different classes of macrophages vary in terms of their function in inflammation. It has been observed that the number of different types of macrophages varies depending on the severity of the SARS-CoV-2 infection. This may lead to a disruption of the precise mechanisms that control inflammation in COVID-19 patients.<sup>31,33</sup> Macrophages in critically ill patients induce the expression of many proteins including IL-6, IL-8, TNF- $\alpha$ , and alarmins. In a mild course of infection, monocytes flow into the alveoli, while in a severe course of the disease, inflammatory monocytes are depleted and degraded, and in their place there is an influx of large numbers of hyperinflammatory monocytes. The last of the mentioned isotypes is responsible for increased secretion of cytokines and chemokines.<sup>31,33</sup>

## Neutrophils

Increased production of cytokines in COVID-19 patients has a stimulating effect on the movement of neutrophils from the vascular space to the alveoli. At the same time, it has been observed that elevated concentration of IL-17, which is responsible for neutrophil activation, may contribute to the development of severe form of the disease.<sup>31,34</sup> Activation of neutrophils leads to increased expression of a number of proteins such as DAMP, chemokines and cytokines. In addition, neutrophils may undergo degranulation during which defensins, myeloperoxidase, lysozyme, etc., are secreted from the inner granules of the cell into the surrounding environment.<sup>31,34</sup> The consequence of this process is intensified production of reactive oxygen species such as H<sub>2</sub>O<sub>2</sub>. Simultaneously, the production of antioxidant enzymes acting as anti-inflammatory proteins, such as superoxide dismutase (SOD), decreases, leading to the development of oxidative stress. Consequently, neutrophil infiltration in the lung tissue may lead to additional damage not only to infected but also to normal cells. Increased cell breakdown induced by neutrophil activity results in an increase in extracellular space (DAMP), triggering a cytokine storm.<sup>31,34,35</sup>

Neutrophils may also be involved in other mechanisms that may trigger pathogen inactivation, including the formation of a neutrophil extracellular trap (NET). This mechanism involves the release of nuclear chromatin fibres derived from neutrophils. At an early stage of activation, the fibres bind to enzymes such as cathepsin G or myeloperoxidase. Such complexes immobilize pathogens and locally concentrate antimicrobial substances, leading to pathogen degradation and thus inhibition of infection.<sup>34,36</sup> Complexes of various enzymes with chromatin fibres may have different functions, including anti-inflammatory – via enzymatic neutralization of cytokines and chemokines.<sup>27</sup> In turn, interactions of NETs with platelets may prove to be potentially dangerous and lead to damage to the vascular endothelial and an increased risk of vascular complications in the course of COVID-19.<sup>36–38</sup>

## Lymphocytes

Lymphocytes are responsible for the adaptive immune response directed to specific components of the pathogen. The complex process of activation begins at the site of primary infection.<sup>31,39</sup> The presence of specific proteins of the viral envelope (E, N, S) is detected by the PRRs of macrophages. Antigen presentation may occur in the bloodstream or in lymphoid organs after antigen-presenting cells (APCs) enter them. These cells, after neutralizing the pathogen in cooperation with dendritic cells, present the virus antigen to naive T lymphocytes. The next step is further maturation and differentiation of naive T cells in the lymphoid organs into CD4<sup>+</sup> and CD8<sup>+</sup> subpopulations. Proliferating Th lymphocytes (CD4<sup>+</sup>) stimulate naive B lymphocytes to transform into plasmocytes that produce antibodies directed against viral antigens. Th lymphocytes secrete antiviral IFN- $\gamma$  in response to viral antigens, leading to its neutralization. They also secrete cytokines, including IL-2, IL-4, and IL-5.<sup>40,41</sup> In contrast, the proliferation and maturation of Tc lymphocytes (CD8<sup>+</sup>) lead to the passage of these cells into the bloodstream. Tc lymphocytes undergo sequestration into the alveoli and airways, where they secrete cytotoxic proteins in response to detection of antigens on the surface of infected cells via MHC class I receptors. Cytotoxic proteins include perforins, granzymes, TNF, TRAIL, etc.<sup>39–41</sup> In patients with a severe course of infection, we observe an impaired lymphocyte response with an accompanying decrease in the lymphocyte count.<sup>39,42,43</sup>

Several mechanisms are responsible for the lymphopenia that occurs in COVID-19 patients. One of them is the migration of Tc lymphocytes to the site of infection as a result of local production of chemokines. As a result of the increased hyperinflammatory response, more cells enter the alveoli, reducing the number of circulating lymphocytes.<sup>39,42,44</sup> Lymphopenia may also develop as a result of infection of lymphocytes with SARS-CoV-2 virus, which may lead to the reaction of T cells (CD8+) and specific antibodies with infected immune cells. Moreover, lymphopenia can be caused by increased lymphocyte apoptosis.<sup>31,39,45</sup> In patients with severe SARS-CoV-2 infection, we observe impaired lymphopoiesis and stimulation of myelopoiesis caused by elevated levels of cytokines such as IL-1, IL-6, IL-27.<sup>39,45,46</sup> Autopsies of patients who died from COVID-19 revealed that the virus was detected in the lung tissue, heart muscle, spleen, kidneys, and intestines. In these patients, tissue damage was quite significant, but this may have been related to the presence of comorbidities. It might be significant that viral RNA was detected in the spleen in all patients. Severe structural abnormalities in this organ were also observed, along with damage to the white pulp in which lymphocytes proliferate.<sup>47–49</sup>

## Platelets

SARS-CoV-2 infection is accompanied by thrombocytopenia. It is assumed that the decrease in platelet count (PLT) may be associated with antibiotic therapy and administration of anticoagulants and anti-inflammatory drugs. However, it may also be related to the role of platelets in fighting infection. It should be noted that thrombocytopenia may be associated with a significant risk due to impaired haemostasis. This process may be accompanied by symptoms such as the appearance of bruises, thrombocytopenic purpura, or impaired blood clotting after injury. PLTs also play a supporting role in fighting infection as they contain pattern recognition receptors (PRRs) that detect pathogens. Binding of the ligand to the receptor leads to platelet activation and secretion of alpha and beta interferons, and interleukins including IL-6, which result in inhibition of platelet production by megakaryocytes. In addition, hyperactive platelets are recognized by the immune system and degraded.<sup>50–53</sup>

Therefore, interferons can inhibit cell proliferation in the bone marrow, with the exception of granulocytes. This is because macrophages, granulocytes and many other cells secrete growth factors such as GM-CSF and G-CSF. At the same time, a “cytokine storm” is observed in patients with a severe condition, in the course of which there is an abundant secretion of, among others, IL-6 and IL-8. Accordingly, a decrease in PLT level is observed due to sensitivity of megakaryocytes to signals that inhibit platelet formation.<sup>50–53</sup>

## Inflammatory Markers in COVID-19

### NLR

Based on the blood count results, we can calculate a number of different ratios that indicate ongoing inflammatory processes in the patient's body. One of them is NLR (neutrophil-to-lymphocyte ratio). It is the ratio of the absolute number of neutrophils to the number of lymphocytes in 1µL of peripheral blood. One of the first reports describing the use of this parameter dates back to 2001<sup>54</sup> when NLR was used to assess the severity of inflammation in patients who had undergone surgery to remove colorectal cancer. The study showed that both invasive procedures and active disease processes, including sepsis, contribute to an increase in NLR value.<sup>54</sup> As already mentioned above, the number of neutrophils secreting pro-inflammatory cytokines increases in patients with COVID-19, particularly in severe and critical course of the disease. This condition is caused by a strong activation of the non-specific cellular response, and promotes the development of lymphopenia. The combination of increased neutrophil count and decreased lymphocyte count contributes to an elevated value of NLR.<sup>31,39,54,55</sup> The advanced course of COVID-19 disease is associated with an imbalance between the levels of neutrophils and lymphocytes. This may be related to the occurrence of a “cytokine storm” in which neutrophils play a significant role as effector cells. It has been observed that the number of neutrophils increases in patients with severe symptoms, while the number of lymphocytes decreases. The neutrophil-to-lymphocyte ratio illustrates the correlation between these two populations, which may be an early indicator of the severe course of the disease.<sup>34,38,56,57</sup>

The study by Maddani et al was one of the few to demonstrate an excellent (AUC = 0.91) predictive value of the NLR parameter as a predictor of COVID-19 severity.<sup>58</sup> Yan et al also obtained in their study a promising value of AUC = 0.945

in their study, with a sensitivity of 97.5% and specificity of 78.1% of NLR for assessing the risk of death of COVID-19 patients. Moreover, they found NLR to be an independent risk factor in predicting death from any cause during hospitalization.<sup>59</sup> Wang et al demonstrated a high value (AUC = 0.963, sensitivity 100%; specificity 84%) of NLR as a predictor of patient death in the course of COVID-19 infection.<sup>60</sup> Ertekin et al also showed that the NLR factor may be useful in predicting patient's risk of death (AUC = 0.930, sensitivity 90.9%, specificity 84.4%).<sup>61</sup> Reports by Bastug et al, Zhao et al, Gujar et al, and Acar et al indicate a good predictive value of the NLR ratio in predicting a patient's condition or its deterioration. The AUC values in the studies of these authors were 0.861, 0.76, 0.86, and 0.816, respectively.<sup>62–65</sup> According to the results obtained by Waris et al and Ramos-Peñafiel et al, there were no statistically significant differences in NLR values between the study and control groups.<sup>66,67</sup> In both studies, the groups were not large enough, so the patients showed a considerable degree of variability within them. The exact data can be found in Table 2.

## PLR

The platelet-to-lymphocyte ratio (PLR) is another parameter calculated from the complete blood count and is referred to as a non-specific marker of inflammation. One of the earliest studies describing PLR involved the evaluation of inflammation in hospital-acquired infections, and changes in PLR values in cases of death in intensive care unit. The researchers demonstrated no statistically significant differences in PLR values compared to fatal and cured cases. However, the observed statistically significant difference in the PLR value indicates that it is more valuable in the group of patients with nosocomial infections compared to those without infections.<sup>84</sup> As already mentioned, platelets – apart from their main haemostatic function – play an indirect role in inflammation. In COVID-19, thrombocytopenia occurs as a result of multiple processes caused by a hyperinflammatory state. This is due to the high levels of pro-inflammatory cytokines and the direct activation of platelets present in the course of infection by fragments of broken cells and viral proteins. Activated PLTs show an increased tendency to aggregate, clot, or degrade. As a result, a decrease in PLR is observed in patients in good or intermediate general condition. In contrast, patients in severe condition experience a significant increase in PLR, which is also associated with a decrease in the number of lymphocytes.<sup>85</sup>

The report by Gujar et al indicates a relatively high diagnostic value (AUC = 0.826) of PLR in predicting the patient's condition due to current inflammation in the course of COVID-19.<sup>64</sup> Acar et al showed a statistically significant difference in PLR values in the groups of survivors vs non-survivors, and a good value of the area under the ROC curve: AUC = 0.742.<sup>65</sup> The researchers indicate the possibility of using this coefficient as an auxiliary measure in prognostic evaluation of a patient's condition and mortality due to COVID-19. Numerous reports confirmed statistically significant differences in PLR values which reached higher levels in patients in severe or critical condition compared to those with a milder course of COVID-19 infection. There are also reports by Bilge et al, Ramos-Peñafiel et al, Cıtu et al, and Fois et al, which showed no differences in PLR values between the control and study groups. The researchers emphasize the need for a further analysis of this parameter in the evaluation of patients' condition (Table 3).<sup>66,67,73,86</sup>

## LMR

Another factor calculated from the complete blood count and used as an indicator for assessing patients' inflammation and condition is the lymphocyte-to-monocyte ratio (LMR). This parameter represents the ratio of lymphocytes to monocytes in 1  $\mu$ L of peripheral blood. The use of LMR in COVID-19 patients may prove effective in assessing the course of the disease. The first mention of LMR appeared in the paper by Merikoulias et al, published in 2010, in which the authors described the application of LMR in the screening diagnosis of viral diseases, ie, influenza.<sup>87</sup> Zhu et al considered LMR as a marker of systemic inflammation in different types of cancer<sup>88</sup> while Ren et al conducted research on the use of LMR as a prognostic factor in patients with cardiovascular disease.<sup>89</sup> COVID-19 patients show increased secretion of inflammatory mediators that enhance immune system functions such as granulopoiesis and monocytopoiesis. These cells become activated during infection and intensely secrete pro-inflammatory cytokines including IL-6, IL-8, TNF, IFN, etc., thus inducing a state of “cytokine storm” that inhibits lymphocytopoiesis. In patients with COVID-19, lymphopenia is observed in laboratory tests, and, in more severe or critical cases, monocytosis, which results in a decrease in LMR.



**Table 2** NLR Ratio in Various Studies.<sup>58–86</sup>

Authors	Study Group N	Control Group N	NLR Values		P value	Cut-off	AUC	Specificity (%)	Sensitivity (%)	Observations
			Study	Control						
Sayed et al <sup>68</sup>	n=701; ICU n=41 non-ICU n=660	n =250	Non-ICU=2.85 ICU=5.5	2.18	<0.0001	5.5	-	23.65	96.4	<ul style="list-style-type: none"> <li>• NLR in connection with history-taking and physical examination may be useful in ruling out the infection.</li> <li>• NLR can be an independent prognostic factor of a severe infection.</li> <li>• Patients with high NLR should be closely monitored and managed.</li> </ul>
Pirsalehi et al <sup>69</sup>	n=243; ICU n=59 Death n=184	Mild and moderate n=1077	8.17 ICU=9.23 Death=5.3	4.45	<0.0001	-	-	-	-	<ul style="list-style-type: none"> <li>• NLR &gt;6.5 may reflect the progression of the disease towards an unfavorable clinical outcome.</li> <li>• NLR &gt; 9 may be a strong death predictor.</li> </ul>
Maddani et al 2021 <sup>58</sup>	n=50	n=142	8.45	2.32	<0.001	5.2	0.91	-	-	<ul style="list-style-type: none"> <li>• Higher incidence of severe disease is observed in older individuals, male, patients with diabetes mellitus, and increased inflammatory parameters such as NLR.</li> <li>• NLR is an independent predictor of disease severity.</li> <li>• NLR may be useful in identification high-risk patients at resource-limited settings and refer them to tertiary care centers for better outcome.</li> </ul>
Jain et al <sup>70</sup>	n=29 Severe	n=162 Non-severe	7.41	3.3	<0.001	4.1	0.779	78	69	<ul style="list-style-type: none"> <li>• NLR is significantly higher in severe COVID-19 patients than non-severe patients.</li> <li>• NLR shows a diagnostic utility in differentiation severe and non-severe cases COVID-19.</li> </ul>

(Continued)

**Table 2** (Continued).

Authors	Study Group N	Control Group N	NLR Values		P value	Cut-off	AUC	Specificity (%)	Sensitivity (%)	Observations
			Study	Control						
Toori et al 2021 <sup>71</sup>	n=169 Symptomatic: Mild n=96, Moderate n=33, severe n=40	n=551 Asymptomatic	Mild=2.08 Moderate=4.79 Severe=9.9	1.92	<0.0001	-	-	-	-	<ul style="list-style-type: none"> <li>NLR is an effective marker to predict and stratify COVID-19 patients as per severity and effectivity.</li> </ul>
Moradi et al 2021 <sup>72</sup>	Severe n=142	Non-severe n=77	5.0	4.1	0.008	-	-	-	-	<ul style="list-style-type: none"> <li>NLR can be a predictor of survival in COVID-19 patients.</li> </ul>
Erdogan et al 2021 <sup>73</sup>	Severe n=36	Non-severe n=268	4.85	2.2	<0.0001	-	-	-	-	<ul style="list-style-type: none"> <li>NLR is significantly higher in severe COVID-19 patients, supporting the fact that it can be a prognostic biomarker.</li> </ul>
Yan et al 2020 <sup>59</sup>	Non-survivors n=40	Survivors n=964	49.06	4.11	0.001	11.75	0.945	78.1	97.5	<ul style="list-style-type: none"> <li>High NLR is associated with poor outcome in critically ill patients with COVID-19.</li> <li>NLR is an independent risk factor for predicting in-hospital all-cause mortality in COVID-19 patients.</li> <li>NLR may be used as a surrogate marker of disease severity at the patient's admission.</li> </ul>
Seyit et al 2020 <sup>74</sup>	Sars-COV-2 Positive n=110	Sars-COV-2 Negative n=123	2.42	1.87	0.007	1.81	0.615	46	70	<ul style="list-style-type: none"> <li>NLR is significantly higher in COVID-19 positive patients than in negative.</li> </ul>
Eslamijouybari et al 2020 <sup>75</sup>	n=520 Cured n=422, Died n=98	n=527	Cured=3.45 Death=6.55	1.56	0.0001	-	0.703	-	-	<ul style="list-style-type: none"> <li>NLR is associated with disease severity and is higher in severe cases of the disease.</li> </ul>

Singh et al <sup>76</sup>	Severe n=93	Non-severe n=108	10.8	7.36	0.0001	-	0.6	60	55	<ul style="list-style-type: none"> <li>NLR calculated at the time of patient's admission has a high predictive value for disease deterioration and adverse clinical outcome.</li> <li>NLR can be used for early stratification of patients.</li> </ul>
	Non-survivors n=91	Survivors n=110	13.15	9.72	0.01	-	-	-	-	
Wang et al 2020 <sup>60</sup>	Non-survivors n=12	Survivors n=119	13.87	1.95		3.338	0.963	84	100	<ul style="list-style-type: none"> <li>NLR is a biomarker reflecting the presence of systematic inflammation, and is associated with all-cause mortality in COVID-19.</li> <li>NLR increase is a useful biomarker to predict the mortality in COVID-19.</li> </ul>
Qin et al 2020 <sup>83</sup>	Severe n=286	Non-severe n=166	5.5	3.2	<0.0001	-	-	-	-	<ul style="list-style-type: none"> <li>NLR may be helpful in the early screening of critical illness, diagnosis and treatment of COVID-19.</li> </ul>
Bastug et al <sup>62</sup>	ICU n=46	Non-ICU n=145	9.04	2.41	<0.001	≥3.21	0.861	62.8	84.4	<ul style="list-style-type: none"> <li>NLR increase seems to be the most powerful laboratory predictor of severe prognosis for COVID-19 and may assist clinicians to identify and follow-up patients with higher risk for progression.</li> </ul>
Ertekin et al 2021 <sup>61</sup>	Died n=220	Survivors n=280	35.43	6.75	<0.001	≥12.1	0.930	84.4	90.9	<ul style="list-style-type: none"> <li>NLR could be a useful predictive parameter for COVID-19 patients.</li> </ul>
Chen et al 2020 <sup>77</sup>	Non-survivors n=104	Survivors n=577	12.27	3.338	0.000	>6.66	-	-	-	<ul style="list-style-type: none"> <li>The combination of NLR and acute myocardial injury on admission is a highly predictive for mortality and survival exclusion diagnosis.</li> <li>NLR &gt;6.66 and myocardial injury require a more aggressive treatment strategy.</li> <li>NLR predicts mortality better than age, LDH, CRP, and lymphocyte levels, suggesting it may be the best predictive parameter (p&lt;0.05).</li> </ul>
Bilge et al 2021 <sup>66</sup>	Cancers n=75	No cancers n=111	7.02	5.52	NS	-	-	-	-	<ul style="list-style-type: none"> <li>There are no significant differences in NLR value between the two compared groups in this study.</li> </ul>

(Continued)

**Table 2** (Continued).

Authors	Study Group N	Control Group N	NLR Values		P value	Cut-off	AUC	Specificity (%)	Sensitivity (%)	Observations
			Study	Control						
Waris et al 2021 <sup>90</sup>	Mild n=52 Moderate n=24 Severe n=9 Critical n=16		Mild=2.7 Moderate=4.95 Severe=5.11 Critical=6.87		<0.001	-	-	-	-	<ul style="list-style-type: none"> <li>NLR may be helpful for clinicians to identify potentially severe cases at early stages, initiate effective management in time, and conduct early triage which may reduce the overall mortality of COVID-19 patients.</li> </ul>
Zhao et al 2020 <sup>63</sup>	Severe n=74	Mild n=211	4.32	2.89	<0.001	3.41	0.76	-	-	<ul style="list-style-type: none"> <li>NLR reflects the intensity of inflammation and is associated with severity of patients with COVID-19.</li> <li>NLR is more useful to predict the severity COVID-19 than other inflammatory markers.</li> </ul>
Gujar et al 2021 <sup>64</sup>	ICU n=264	Isolation n=577	10.9	2.9	0.001	3.6	0.86	-	-	<ul style="list-style-type: none"> <li>NLR can predicts severe illness with high accuracy.</li> </ul>
López-Escobar et al 2021 <sup>78</sup>	Non-survivors n=321	Survivors n=1767	8.7	3.8	<0.0001	6.63	-	74	62	<ul style="list-style-type: none"> <li>NLR is usefulness as a prognostic marker of inflammation in patients who died due to COVID-19.</li> </ul>
Velazquez et al 2021 <sup>79</sup>	ICU n=185	Non-ICU n=2069	6.9	4.1	<0.0001	4.93	-	58	68	<ul style="list-style-type: none"> <li>Patients requiring ICU admission have significantly higher NLR value at the time of hospital admission compared to patients not requiring ICU admission.</li> <li>Higher values of NLR are associated with ICU entry only for strata with SaO<sub>2</sub> &gt; 90%, male sex and age &lt; 70 years.</li> </ul>
Acar et al 2020 <sup>65</sup>	Non-survivors n=19	Survivors n=129	21.0	9.4	≤0.05	10.9	0.816	76.7	73.6	<ul style="list-style-type: none"> <li>NLR is associated with disease mortality and can be used to predict disease progression and mortality.</li> <li>NLR reflects intensity of inflammation and also indicates a poor prognosis.</li> </ul>

Ramos-Penafiel et al 2020 <sup>67</sup>	Death n=54	Alive n=71	13.93	10.56	0.052	-	-	-	-	<ul style="list-style-type: none"> <li>NLR can predicts SARS-CoV-2 infection-associated mortality.</li> </ul>
Kilercik et al 2021 <sup>80</sup>	Critical-survivors severe n=23 Critical non-survivors; death n=15	Non-critical mild n=59	Critical-survivors severe=6.2 Critical non-survivors; death=11.4	Non-critical Mild=2.67	<0.001	3.1	-	54.1	87	<ul style="list-style-type: none"> <li>NLR is the best time-related marker over the course of the disease, distinguishing non-critical patient group from non-survivor patient group after the 2th-4th day of admission</li> <li>NLR can be used as an indicator to distinguish critical patients from non-critical COVID-19 patients and to predict mortality from COVID-19.</li> </ul>
						4.4	-	68.2	78.5	
Citu et al 2022 <sup>81</sup>	Deaths n=17	Survivors n=91	13.83	8.31	0.001	9.1	0.689	67	70	<ul style="list-style-type: none"> <li>NLR determined at hospital admission have a high value in predicting mortality in patients with COVID-19.</li> </ul>
Moisa et al 2021 <sup>82</sup>	Group 1 - patients on IMV upon ICU admission n=33 group -2 IMV during ICU-LOS n=134 Group 3 - non-IMV during ICU-LOS n=105	Survivors n=130	G1=22.76 G2=22.46 G3=8.95	9.5	<0.0001	-	-	-	-	<ul style="list-style-type: none"> <li>NLR is the best independent predictor for invasive mechanical ventilation need and death.</li> </ul>
	Non-survivors n=142		24.4			-	-	-	-	
Fois et al 2020 <sup>86</sup>	Non-survivors n=29	Survivors n=90	9.17	5.00	0.0015	15.2	0.697	97	38	<ul style="list-style-type: none"> <li>NLR increases in severe COVID-19 disease patients and is associated with disease severity.</li> <li>NLR have a high value in predicting disease severity.</li> <li>NLR is also associated with survival.</li> </ul>

**Abbreviations:** ICU, intensive care unit patients; non-ICU, non-Intensive care unit patients; IMV, invasive mechanical ventilation; ICU-LOS, ICU length of stay.



**Table 3** PLR Ratio in Various Studies.<sup>63–86</sup>

Authors	Study Group N	Control Group N	PLR Values		P value	Cut-off	AUC	Specificity (%)	Sensitivity (%)	Observations
			Study	Control						
Bilge et al 2021 <sup>66</sup>	n=75 (Cancers)	n=111 (No cancers)	303.89	242.56	NS	-	-	-	-	<ul style="list-style-type: none"> <li>There is no statistically significant differences in the PLR ratio between the control group and the study group.</li> </ul>
Waris et al 2021 <sup>90</sup>	Mild n=52 Moderate n=24 Severe n=9 Critical n=16		Mild=131.5 Moderate=180.6 Severe=139.5 Critical=238.3		<0.001	-	-	-	-	<ul style="list-style-type: none"> <li>PLR can be helpful for clinicians to identify potentially severe cases at early stages, initiate effective management in time, and conduct early triage which may reduce the overall mortality of COVID-19 patients.</li> </ul>
Zhao et al 2020 <sup>63</sup>	Severe n=74	Mild n=211	237	229	<0.001	274	0.69	-	-	<ul style="list-style-type: none"> <li>PLR reflects the intensity of inflammation and is associated with severity of patients with COVID-19.</li> </ul>
Gujar et al 2021 <sup>64</sup>	ICU n=264	ISOLATION n=577	28.4	9.5	0.001	9.4	0.826	-	-	<ul style="list-style-type: none"> <li>PLR can predict severe illness with high accuracy.</li> </ul>
López-Escobar et al 2021 <sup>78</sup>	Non-survivors n=321	Survivors n=1767	2.4	1.9	<0.0001	2.98	-	78	44	<ul style="list-style-type: none"> <li>PLR is higher at admission in patients who died compared with patients who survived, but they do not maintain significance after more complex model of multivariable adjustment.</li> </ul>
Velazquez et al 2021 <sup>79</sup>	ICU n=185	Non-ICU n=2069	2.0	1.9	0.023	2.5	-	66	47	<ul style="list-style-type: none"> <li>PLR shows no significant association with ICU admission in the stratified analysis.</li> </ul>
Acar et al 2020 <sup>65</sup>	Non-survivors n=19	Survivors n=129	427.9	261.5	≤0.05	289.9	0.742	68.9	57.8	<ul style="list-style-type: none"> <li>PLR is associated with disease mortality and can be used to predict disease progression and mortality.</li> <li>Increased PLR reflects an inflammation and can also indicates a poor prognosis.</li> <li>PLR in COVID-19 can assist in the diagnosis of prediction of mortality.</li> </ul>

Ramos-Peñafiel et al 2020 <sup>67</sup>	Death n=54 0648	Alive n=71	419	338	0.192	-	-	-	-	<ul style="list-style-type: none"> <li>• PLR can predicts SARS-CoV-2 infection-associated mortality.</li> <li>• PLR may be used in combination as indicators of the inflammatory and immunological status.</li> </ul>
Citu et al 2022 <sup>81</sup>	Deaths n=17	Survivors n=91	345 ± 235	324 ± 219	0.71	-	-	-	-	<ul style="list-style-type: none"> <li>• AUC for PLR have no statistically significant discriminatory value.</li> </ul>
Moisa et al 2021 <sup>82</sup>	Group 1 -patients on IMV upon ICU admission n=33 Group -2 IMV during ICU-LOS n=134 Group 3 - non-IMV during ICU-LOS n=105		Group 1=489 Group 2=566 Group 3=342		<0.0001	-	-	-	-	<ul style="list-style-type: none"> <li>• PLR is found to be an independent predictor for IMV need, but with lower hazard ratio value.</li> </ul>
	Non-survivors n=142	Survivors n=130	G: 579 K: 351		<0.0001	-	-	-	-	
Fois et al 2020 <sup>86</sup>	Non-survivors n=29	Survivors n=90	265	214	0.24	240	0.572	58	59	<ul style="list-style-type: none"> <li>• There are no statistically significant differences in PLR ratio between the control group and the study group.</li> <li>• PLR ratio shows a lower diagnostic efficiency than SII.</li> </ul>
Jain et al 2021 <sup>70</sup>	Severe n=29	Non-severe n=162	204	121	<0.001	115.3	115.3	62	79	<ul style="list-style-type: none"> <li>• PLR is significantly higher in severe COVID-19 patients than non-severe patients.</li> <li>• The cut off for PLR is 115.3 and can classify the patients into severe and non-severe categories.</li> </ul>

**Abbreviations:** ICU, intensive care unit patients; non-ICU, non-intensive care unit patients; IMV, invasive mechanical ventilation; ICU-LOS, ICU length of stay.

Zhao et al demonstrated a good diagnostic value of the LMR (AUC = 0.73) in differentiating the course of the disease with accompanying inflammation severity. The researchers observed higher LMR value in patients infected with SARS-CoV-2 compared to those with Influenza A virus.<sup>64</sup> Citu et al obtained satisfactory prognostic value of LMR (AUC = 0.69) in the assessment the risk of death of patients hospitalised in the course of COVID-19.<sup>73</sup> Waris et al, Ramos-Peñafiel et al, and Moisa et al observed a decrease in the value of the ratio with the severity of the disease.<sup>67,74,90</sup> However, Bilge et al and Fois et al showed no statistically significant differences in LMR values between patients with different clinical status (Table 4).<sup>66,86</sup> Such inconclusive results indicate the need for further analysis of LMR in COVID-19.

## SII

One of the new indicators for assessing systemic inflammation is the systemic immune-inflammation index (SII). This parameter is calculated by multiplying the number of platelets and neutrophils divided by the number of lymphocytes. Initially, SII was analysed for its prognostic value in patients with hepatocellular carcinoma (HCC). Researchers showed that higher SII values in the perioperative period may be correlated with a worse prognosis of the disease. The condition was associated with enhanced inflammation in hepatocellular carcinoma lesions. They also demonstrated that 85% of the study group with increased SII values had HBV infection.<sup>91</sup> Another report on SII concerned the evaluation of prognosis in patients with small cell lung cancer (SCLC). It showed a significantly higher level of SII in patients with SCLC. Such results, according to the researchers, were related to increased inflammation caused by strong activation of the immune system.<sup>92</sup> Chu et al showed elevated SII values in patients with acute myocardial infarction. The course of myocardial infarction is associated with complex processes leading to increased breakdown of endothelial cells of blood vessels in the heart as well as breakdown of myocytes in the ischemic area. This leads to an intensification of the inflammatory response, which leads to an increase in, among others, number of neutrophils, monocytes, and platelets in the circulating pool.<sup>93</sup> Similarly, in the course of COVID-19, there are dynamic changes in the patient's clinical condition as a result of an increased non-specific cellular response, as in the other diseases mentioned above.

The study by Gujar et al showed a very high diagnostic value of the SII parameter (AUC = 0.841) in differentiating the severity of the course of the disease caused by the SARS-CoV-2 virus. The mean value of SII in seriously ill and critically ill patients hospitalized in the ICU was 2484, and in the control group in home or hospital isolation: 653.3 ( $p = 0.001$ ).<sup>64</sup> A high diagnostic value was observed by Hamad et al, in which the area under the ROC curve (AUC) was 0.819. The study group of critically ill patients hospitalized in the ICU had a mean SII value of 2016.29, while patients who did not require ICU hospitalization had a mean SII value about four times lower: 492.29. In addition, the researchers obtained a diagnostic sensitivity of SII of 50.9%, and specificity – 95.6% in assessing the risk of worsening of the condition of COVID-19 patients, and thus also hospitalization in the ICU.<sup>94</sup> Zhao et al showed that the SII shows a good diagnostic value in predicting the exacerbation of a patient's condition (AUC = 0.72). The studied SII coefficient, together with other biochemical markers, including IL-6, as well as haematological markers and calculated ratios, including NLR and PLR, may be useful in assessing the severity of inflammation (intensity may be related to an inflammatory response) and thus the patient's condition.<sup>63</sup> Moreover, a study by Acar et al demonstrated the diagnostic utility of SII in determining the risk of death of COVID-19 patients (AUC = 0.733).<sup>65</sup> SII values were significantly higher in patients whose disease led to death compared to those who recovered.<sup>65</sup> These results may indicate that a strong non-specific cellular response may be accompanied by a significant increase in inflammation and thus a worse clinical condition of the patient. However, there are reports by Bilge et al and Citu et al, in which no statistically significant differences in SII values were observed in COVID-19 patients with different clinical conditions (Table 5).<sup>66,73</sup>

## Conclusions

In COVID-19, we observe a significant dynamics of changes in the clinical condition of patients, caused by hyperactivation of the immune system. This mechanism is associated with numerous changes in laboratory tests, which is particularly visible in biochemical and haematological parameters. Complete blood count which quantitatively and qualitatively evaluates blood cell populations has proven to be a commonly used and effective tool for assessing the clinical condition of a patient. Factors such as NLR, LMR, PLR or SII, calculated on the basis of the number of

**Table 4** LMR Ratio in Various Studies. <sup>63–98</sup>

Authors	Study Group N	Control Group N	LMR values		P value	Cut Off	AUC	Specificity (%)	Sensitivity (%)	Observations
			Study	Control						
Bilge et al 2021 <sup>66</sup>	Cancers n=75	No cancers n=111	0.16	0.14	NS	-	-	-	-	• There is no significant differences in LMR between the two groups compared in this study.
Waris et al 2021 <sup>90</sup>	Mild n=52 Moderate n=24 Severe n=9 Critical n=16		Mild= 8.32 Moderate=5.74 Severe=5.54 Critical=4.37		0.011	-	-	-	-	• LMR can be useful for clinicians to identify potentially severe cases at early stages, initiate effective management in time, and conduct early triage which may reduce the overall mortality of COVID-19 patients.
Zhao et al 2020 <sup>63</sup>	Severe n=74	Mild n=211	1.88	3.13	<0.001	3.13	0.73	81%	58%	• LMR reflects the intensity of inflammation and is associated with severity of patients with COVID-19.
Ramos-Peñafiel et al 2020 <sup>67</sup>	Death n=54	Alive n=71	0.53	0.37	0.004	-	-	-	-	• MLR can predict SARS-CoV-2 infection-associated mortality.
Citu et al 2022 <sup>81</sup>	Deaths n=17	Survivors n=91	0.83	0.53	0.01	0.69	0.661	74%	58%	• MLR determined at hospital admission have a high value in predicting death among patients with COVID-19.
Moisa et al 2021 <sup>82</sup>	Non-survivors n=142	Survivors n=130	0.69 ± 0.4	0.61 ± 0.44	0.017	-	-	-	-	• MLR shows a little effectiveness in assessing the risk of death.
Fois et al 2020 <sup>86</sup>	Non-survivors n=29	Survivors n=90	0.429	0.333	0.058	-	-	-	-	• Changes in the MLR value between the control group and the study group are not sufficient to demonstrate statistical significance.
Çalışkan et al 2022 <sup>95</sup>	Severe (n = 113)	Non-severe (n = 435)	0.36	0.5	0.001	≤0.49	0.605	50.89	73.15	• MLR is higher in the severe group compared to non-severe group of patients with COVID-19.

(Continued)

**Table 4** (Continued).

Authors	Study Group N	Control Group N	LMR values		P value	Cut Off	AUC	Specificity (%)	Sensitivity (%)	Observations
			Study	Control						
Noor et al 2020 <sup>96</sup>	Severe n=370	Non-severe n=365	6.635	10.548	<0.001	-	0.262	-	-	<ul style="list-style-type: none"> <li>LMR could not be a diagnostic factor for severity of disease because the AUC was less than 0.50.</li> </ul>
Lissoni et al 2020 <sup>97</sup>	n=17	n=100	2.7	5.8	<0.001	-	-	-	-	<ul style="list-style-type: none"> <li>LMR values are abnormally low and LMR mean values observed in COVID-19 patients were significantly lower than in the control group.</li> </ul>
Eissa et al 2021 <sup>98</sup>	n=88	n=41	3.94	5	<0.001	6	0.738	65.9	71	<ul style="list-style-type: none"> <li>LMR have a high sensitivity (71%, cutoff &lt;6).</li> </ul>
Anurag et al 2020 <sup>44</sup>	Mild=116 Moderate=12 Severe=20		Mild=5.16 Moderate=3.16 Severe = 5.14		0.565	-	-	-	-	<ul style="list-style-type: none"> <li>There are no statistically significant differences in the LMR values in patients with different clinical conditions in COVID-19.</li> </ul>

**Abbreviations:** ICU, intensive care unit patients; non-ICU, non-intensive care unit patients; IMV, invasive mechanical ventilation; ICU-LOS, ICU length of stay; MLR, monocytes to lymphocytes ratio.



**Table 5** SII in Various Studies [63–85]

Authors	Study Group N	Control Group N	SII values		P value	Cut Off	AUC	Specificity (%)	Sensitivity (%)	Observations
			Study	Control						
Bilge et al 2021 <sup>66</sup>	Cancers n=75	No cancers n=111	1733.5	1445.58	NS	-	-	-	-	• SII is not a sensitive prognostic tool in patients with COVID-19 in the presence of malignancy.
Zhao et al 2020 <sup>63</sup>	Severe n=74	Mild n=211	1032	654	<0.001	1091	0.72	-	-	• SII reflects the intensity of inflammation and is associated with severity of patients with COVID-19.
Gujar et al 2021 <sup>64</sup>	ICU n=264	Isolation n=577	2484	653.3	0.001	799.2	0.841	-	-	• SII can predict severe course of COVID-19 with high accuracy.
López-Escobar et al 2021 <sup>80</sup>	Non-survivors n=321	Survivors n=1767	16.4	8.5	<0.0001	13.87	-	71	57	• Patients who died presented significantly higher SII at admission compared with patients who survived, but they did not maintain significance after more complex model of multivariable adjustment.
Velazquez et al 2021 <sup>81</sup>	ICU n=185	Non-ICU n=2069	13	9.2	<0.0001	12.26	-	64	54	• Patients requiring hospitalization in IU with worse clinical condition had higher SII index values than patients with better clinical condition.
Acar et al 2020 <sup>65</sup>	Non-survivors n=19	Survivors n=129	4426	2445	≤0.05	2699	0.733	77.5	68.4	<ul style="list-style-type: none"> <li>• SII is associated with disease mortality and can be used to predict disease progression and mortality.</li> <li>• Increased SII, which reflect inflammation, can also indicate a poor prognosis.</li> <li>• Inflammatory parameters such as SII in COVID-19 can assist in the diagnosis of prediction of mortality.</li> </ul>
Citu et al 2022 <sup>81</sup>	Deaths n=17	Survivors n=91	2789	2183	0.23	-	-	-	-	• AUC for and SII had no statistically significant discriminatory value.

(Continued)

**Table 5** (Continued).

Authors	Study Group N	Control Group N	SII values		P value	Cut Off	AUC	Specificity (%)	Sensitivity (%)	Observations
			Study	Control						
Moisa et al 2021 <sup>82</sup>	Group 1 - patients on IMV upon ICU admission n=33 Group 2 - IMV during ICU-LOS n=134 Group 3 - non-IMV during ICU-LOS n=105		G1=6148 G2=6552 G3=2802		<0.0001	-	-	-	-	<ul style="list-style-type: none"> <li>SII is a good independent predictor for invasive mechanical ventilation need and death as well as is strongly correlated with respiratory failure severity and systemic inflammation and can be used as a biomarker for disease severity and progression, triage, and outcome.</li> </ul>
	Non-survivors n=142	Survivors n=130	6875	3068	<0.0001	-	-	-	-	
Fois et al 2020 <sup>86</sup>	Non-survivors n=29	Survivors n=90	1854	1022	0.039	1835	0.628	75	55	<ul style="list-style-type: none"> <li>SII is the most significant prognostic biomarker for survival in patients with SARS-CoV2-infected patients when compared to other widely employed blood cell count-derived inflammation indexes such as the NLR, dNLR, PLR, MLR, NLPR, MPR, AISI, and SIRI.</li> <li>Properly designed prospective studies should be performed to confirm the prognostic ability of SII in COVID-19 patients and its utility in the early identification of high-risk patients and the implementation of optimal individualized treatment strategies.</li> </ul>
Hamad et al 2022 <sup>94</sup>	ICU n=310	Non-ICU n=185	2016.29	492.29	<0.0001	1346	0.819	95.6	50.9	<ul style="list-style-type: none"> <li>SII was linked to survival rather than admission to ICU.</li> </ul>

**Abbreviations:** ICU, intensive care unit patients; non-ICU, non-intensive care unit patients; IMV, invasive mechanical ventilation; ICU-LOS, ICU length of stay.

individual blood cell populations, may prove useful to clinicians in assessing the patient's condition and the severity of inflammation in the course of COVID-19. The advantage of determining ratios is also easy interpretation of the calculated parameters, low cost, and routine blood counts at specific intervals.

Numerous studies indicate the high diagnostic value of NLR in assessing the severity of inflammation in the course of infection caused by the SARS-CoV-2 virus. The NLR was higher in patients with a worse clinical condition than mild and moderate as well as in patients who died from COVID-19. This suggests that this ratio can be used as a parameter to assess the risk of health deterioration or death. Furthermore, PLR was statistically significant higher in patients in severe than moderate clinical condition and should be evaluated together with other inflammatory markers. The SII ratio has been proven to be effective in evaluating a patient's condition. This marker can be very useful in assessing the severity of the disease course and, for example, in the initial selection of optimal therapy. The fewest studies concerned the evaluation of the diagnostic utility of the LMR parameter. Despite the occurrence of an inflammatory response in the course of the disease, patients do not always demonstrate changes in LMR values. On the other hand, some studies show a decrease in the level of LMR in patients with a more severe course of the disease. However, currently there are still relatively few reports clearly confirming the effectiveness of analysed ratios, which should be taken into account in further research.

## Data Sharing Statement

All data generated or analysed during this study are included in this published article.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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