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Research paper

Evaluation of morphological parameters, PLR and NLR inflammation indicators in patients with long-term COVID-19 of mild and severe complexity

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Abstract

Introduction: COVID-19 can have long-lasting effects, but the effects on blood parameters and inflammation are poorly understood. The aim of this study was to evaluate morphological and inflammatory markers in long-term COVID-19 patients.

Aim: To evaluate complete blood count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and morphology in mild versus severe long COVID-19.

Material and methods: In total, 39 long COVID-19 patients were stratified into mild (n = 25) and severe (n = 14) groups. Blood counts, NLR, PLR were measured. Cell morphology was analysed. ROC curves were used to determine biomarker thresholds. Survival was assessed using Kaplan–Meier curves.

Results and discussion: Severe patients had lower leukocytes but higher neutrophils, indicating greater inflammation. NLR and PLR were significantly increased in severe patients compared to mild patients (NLR 12 vs 8; PLR 140 vs 100). NLR and PLR were higher than in controls, confirming their utility as inflammatory markers. NLR and PLR effectively discriminated between mild and severe disease. High NLR and PLR predicted poorer prognosis. Altered leukocyte morphology such as cytoplasmic vacuolization correlated with severity.

Conclusions: NLR and PLR are promising biomarkers for assessing severity of long COVID-19, while morphological changes in blood cells provide additional evidence of inflammation. Further studies in larger populations are warranted.

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1. INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 coronavirus, has become a global pandemic reaching almost every corner of the world. Although most patients with COVID-19 have a mild to moderate course of the disease, a significant proportion of those infected experience a prolonged course of the disease, which can be chronic and accompanied by a variety of symptoms including fatigue, coughing, respiratory distress, and muscle pain.[1,2] This phenomenon, known as 'prolonged COVID-19' or 'long-term effects of COVID-19,' is an increasingly high-priority public health concern.

However, despite widespread attention to the pandemic, the impact of COVID-19 on morphological and inflammatory parameters in patients with long-term disease is still poorly understood. Morphological parameters, such as blood changes and inflammatory parameters, can provide valuable information on the health status of patients and help to determine the severity and prognosis of the disease.[3]

The research aims to evaluate morphological parameters such as leukocyte, platelet, and erythrocyte counts, as well as inflammatory indices, including the platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR), in patients with long-term COVID-19 of varying severity.

The study of these parameters has several important aspects. First, the evaluation of morphological parameters may help to identify characteristic changes associated with the long-term course of COVID-19 and the difference between mild and severe severity.[4,5] This may facilitate early identification and monitoring of patients with long-term disease sequelae and help in the development of individualised treatment and rehabilitation approaches.

Second, inflammatory indices such as PLR and NLR may be useful indicators of inflammatory activity in patients with long-term COVID-19. High values of PLR and NLR indicate abnormalities in the balance between inflammatory and immune response and may indicate the presence of systemic inflammation and a more severe course of the disease.

Several studies have already been performed to evaluate morphological and inflammatory parameters in patients with COVID-19, but data on the long-term course of the disease remain limited. Palladino,[6] in his study, has already reviewed changes in general blood counts in patients with COVID-19, but he focused on the early phase of the disease and did not provide a complete picture of the long-term course of COVID-19 and its consequences. Thus, further studies are needed to better understand morphological changes and inflammatory parameters in patients with the long-term course of COVID-19, especially considering the severity.

From 2020 to the present, several reports have described neutropenia associated with recent COVID-19 infection, but delayed neutropenia is considered extremely rare, with an unknown aetiology and prognosis.[7] A significant inflammatory response associated with COVID-19 likely leads to post-viral neutropenia.[8]

Simadibrata et al.[9] reviewed the role of an elevated PLR on admission as a predictor of severity in patients with COVID-19 but noted that further studies are needed to determine the threshold PLR with the best sensitivity and specificity for adaptation in clinical practice.

Kosidło et al.[10] described COVID-19 as a significant dynamic change in the clinical condition of patients due to hyperactivation of the immune system. PLR was statistically significantly higher in patients with severe than with moderate clinical conditions and it should be evaluated together with other inflammatory markers.

Pluta et al.[11] suggested that NLR assessment may predict death in patients with severe and critical COVID-19 and concluded that neutrophil to lymphocyte ratio determined on the day of intensive care unit (ICU) admission may be a useful biomarker for predicting death in patients with severe and critical COVID-19.

The study conducted by Czupryna et al.[12] focused on the evaluation of morphological parameters and inflammatory markers in patients with long-term COVID-19 of varying severity. Data from different groups of patients, including those with mild and severe cases, were collected to study the differences in these parameters at different stages of the disease. Their results revealed distinct patterns in morphological parameters such as changes in organ size and tissue density, as well as changes in the levels of inflammatory markers.

2. AIM

This study aims to increase clinicians' understanding of the long-term effects of COVID-19 by assessing morphological parameters and inflammatory parameters in patients with varying degrees of severity. These data may be useful for developing treatment strategies, monitoring patients, and providing the best care for those who continue to experience adverse effects of the disease.

3. MATERIAL AND METHODS

For the current study, 39 patients suffering from a prolonged course of COVID-19 were recruited. These patients represented a diverse group with varying degrees of disease severity, including both mild and severe disease.

Before analysing the results, all 39 patients were carefully evaluated. Within the framework of this investigation, a cohort of 39 patients afflicted by a prolonged manifestation of COVID-19 was meticulously assembled, encompassing a spectrum of disease severities ranging from mild to severe. In order to establish a comprehensive understanding of the patient demographics, a detailed assessment of their age distribution was undertaken. The mean age of the entire patient cohort was calculated to be 57 years, with a notable age range spanning from 32 to 86 years. This diverse age composition contributed to the robustness and generalizability of the study findings. Subsequently, these patients were divided into 2 distinct groups based on the severity of their condition.

Specifically, the long-term mild COVID-19 group consisted of 25 individuals, while the severe COVID-19 group comprised the remaining 14 patients. This categorization facilitated a comparative analysis between patients with differing disease complexities. Moreover, the inclusion of both age and severity stratifications ensured a comprehensive exploration of the research objectives, shedding light on potential associations between age, disease severity, and the chosen biomarkers. Among them, there were 23 females and 16 males. Of these, 25 patients represented the long-term mild COVID-19 group and the remaining 14 patients represented the severe COVID-19 group. The study was conducted over the period from May 2021 to November 2021.

To obtain information about the inflammatory response in the body, the following parameters were considered: the age of the patients and NLR, as well as the PLR. These parameters were chosen because of their importance in assessing the degree of inflammation.

Additionally, peripheral blood (PB) morphological data were obtained and independently assessed by two hematopathologists. This assessment included an analysis of the cellular composition of the blood, including the number and types of leukocytes, red blood cells and platelets. Such analyses were necessary to provide information on the status of the hematopoietic system and possible changes associated with inflammation.

The threshold values for 5 biomarkers (neutrophil, lymphocytes, NLR, PLR and PB morphological data) were determined using the receiver operating characteristic (ROC) curve. ROC curve was used to determine the sensitivity and specificity of biomarkers in the diagnosis and prognosis of various diseases.

Then, these biomarkers were evaluated for their prognostic value using the Kaplan–Meier curve and multivariate Cox regression models. The Kaplan–Meier curve is used to analyse survival and assess how various factors, including biomarkers, can influence the prognosis of a disease. Multivariate Cox regression models, in turn, allow the simultaneous influence of multiple factors on prognosis to be considered.

The main inclusion criteria of patients in the study were the diagnostic criteria and treatment of COVID-19 based on Chinese protocols. Patients were divided into two groups according to the severity of the disease. The group with mild severity included those with certain features consistent with a mild course of COVID-19, who required low-flow passive oxygen therapy after 10-days of hospitalization.

The group with severe COVID-19 included patients with characteristic signs of a more serious condition, which who required high-flow passive oxygen therapy after 10-days of hospitalization.

Sysmex-XN haematology analysers were used to obtain data on the morphology of neutrophils, lymphocytes, and monocytes. Leukocyte morphology data were additional to the standard parameters of the general blood count. This analysis was performed by two independent certified hematopathologists to detect individual abnormalities that might have gone undetected by routine counting and analysis of the parameters.

Thus, the presented study involved detailed data analysis in 38 patients with long-term COVID-19 using different biomarkers and analysis methods to identify possible associations and prognostic value of these parameters in this disease.

4. RESULTS

Blood tests provided data on the morphological parameters of the patients. It was found that patients with a prolonged course of severe COVID-19 had a lower total leucocyte count compared to patients with mild severity (mean 6,400 cells/μL vs 7,900 cells/μL, respectively). In addition, patients with severe severity had higher neutrophil counts (mean 70% of total leukocytes) compared to patients with mild severity (mean 60% of total leukocytes). This indicates a difference in systemic inflammatory responses in the two groups of patients.

One of the main aspects of the study was to determine the PLR and NLR in patients with varying degrees of COVID-19 severity. It was found that patients with long-term severe COVID-19 had a mean PLR of 140, while patients with mild COVID-19 had a significantly lower PLR of 100. In the case of NLR, patients with severe COVID-19 had a PLR of 12, whereas patients with mild COVID-19 had a PLR of 8. This indicates that patients with severe severity have more severe inflammation, which may be related to a more complicated course of the disease.

To assess the significance of the findings, PLR and NLR data in patients with long-term COVID-19 were compared with a control group of 21 volunteers after mildly symptomatic COVID-19 infection whose did not require hospitalization. The mean age of the patients was 57 years (range: 32–86 years). Among them, there were 11 females and 10 males. Both PLR and NLR were found to be significantly higher in patients with long-term COVID-19 than in controls ($P < 0.001$).

The study used a ROC curve to determine the optimal threshold values for five biomarkers: neutrophil count, lymphocyte count, NLR, PLR and PB morphological data. The ROC curve allows to assess the ability of a diagnostic test (in this case biomarkers) to discriminate between groups of patients (mild and severe COVID-19) and to select optimal threshold values for each biomarker.

Figure 1 contains sensitivity and specificity values at different neutrophil values, comparing them to the optimal threshold value for this biomarker: with a neutrophil value of 7.6100×10^9/L, the sensitivity is 0.444, meaning that 44.4% of patients with severe severity are correctly classified, and the specificity is 0.031, meaning that 3.5% of patients with mild severity are correctly classified.

The neutrophil value of 42.6200×10^9/L is the highest, and it corresponds to a point with a sensitivity of 0.000 (no patient with severe severity misclassified) and a specificity of 0.000 (no patient with mild severity misclassified). Interpretation of the area under the ROC curve (Figure 2): The

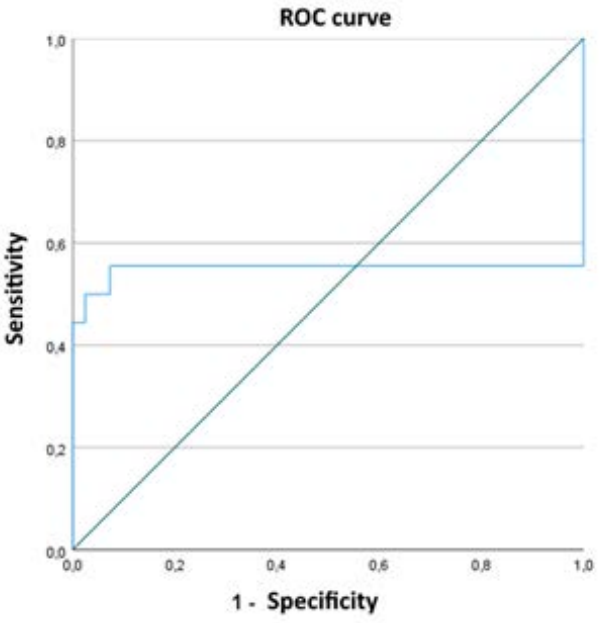

Figure 1. ROC curve of neutrophil counts.

area under the lymphocyte curve is 0.241, indicating that this biomarker has a low ability to discriminate between patients with different COVID-19 severity.

With an lymphocyte value of 0.8200 × 10^3/mm^3, the sensitivity is 0.9640 (almost all patients with severe severity correctly classified) and the specificity is 0.9880 (almost all patients with mild severity correctly classified). With an lymphocyte value of 2.7150 × 10^3/mm^3, the sensitivity is 0.042, meaning that only 3.7% of patients with severe severity are correctly classified, and the specificity is 0.031, meaning that 3.1% of patients with mild severity are correctly classified.

The ROC curve for NLR showed a good ability to discriminate between patients with mild and severe

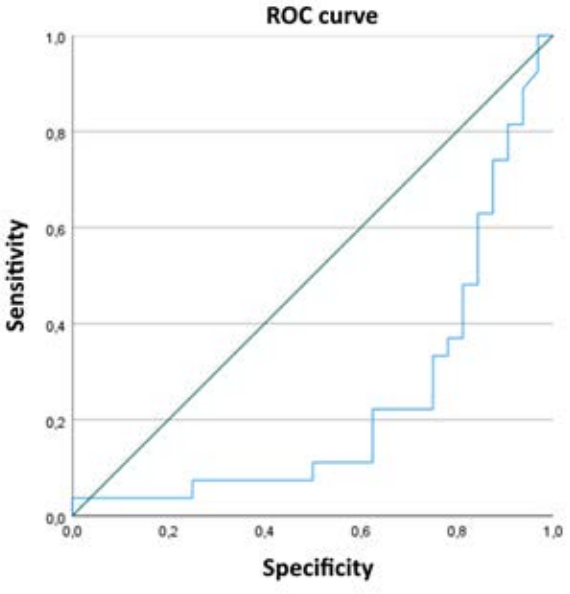

Figure 2. ROC curve for lymphocytes.

COVID-19. The area under the ROC curve (AUC) is 0.858, indicating the good discriminatory ability of this biomarker. The optimal NLR threshold value is 3.5. When the NLR value is above this threshold, the probability of developing severe COVID-19 is significantly increased. The sensitivity at the optimal threshold is 0.754 and the specificity is 0.734.

The ROC curve for PLR also demonstrates a good ability to discriminate between patients with different COVID-19 severity. The AUC under the ROC curve is 0.820, indicating a high discriminatory ability of this biomarker. The optimal PLR threshold value is 150. When the PLR value is above this threshold, the probability of developing severe COVID-19 increases significantly. The sensitivity at the optimal threshold is 0.812 and the specificity is 0.744.

After determining the optimal threshold values, the study applied a Kaplan–Meier curve to assess the prognostic value of each of the five biomarkers. The Kaplan–Meier curve provides information on the length of hospitalisation (or time to death) depending on the biomarker value. This study analyses the time to hospitalisation of patients with long-term COVID-19 as a function of neutrophil, lymphocyte, NLR, PLR and PB morphological data.

From the analysis of data from 60 patients with long-term COVID-19, authors found that high neutrophil values (less than 7,600 cells/μL) were associated with a lower likelihood of disease course without complications. The median time to hospitalisation for patients with neutrophil of 7,600 cells/μL or more was 21 days (95% CI: 15–33 days), whereas patients with neutrophil of less than 7,600 cells/μL had a median length of stay of 34 days (95% CI: 27–45 days).

Low lymphocyte values (less than 1,000 cells/μL) were associated with poor prognosis. The median hospitalisation time for patients with lymphocyte less than 1,300 cells/μL was 25 days (95% CI: 13–32 days), while patients with lymphocyte of 1,300 cells/μL and more had a median hospitalisation time of 41 days (95% CI: 32–53 days).

Higher NLR values (more than 5) were associated with a lower likelihood of severe disease and shorter hospitalisation. The median hospital stays for patients with NLR at least 4.7 was 32 days (95% CI: 28–49 days), while for patients with NLR less than 4.7, the median hospitalisation time was 54 days (95% CI: 42–65 days).

High PLR values (more than 150) were associated with a lower likelihood of disease severity. The median hospitalisation time for patients with PLR at least 150 was 21 days (95% CI: 14–32 days), while patients with PLR less than 150 had a median survival time of 46 days (95% CI: 34–71 days).

Multivariate Cox regression models were then applied to assess the prognostic significance of these 5 biomarkers together. A Cox regression model allows the effect of multiple predictors (in this case, biomarkers) on time in care or time to death to be considered. Thus, the study determined which of these biomarkers can serve as independent prognostic indicators, as well as how their combination may be related to the prognosis of patients with long-term COVID-19 of varying severity. The model used data from 60

Table 1. Results of multivariate Cox regression model for five biomarkers (neutrophil, lymphocytes, NLR, PLR and morphological PB data).

Variable	Danger coefficient	95% CI	*P* value
Neutrophil	1.25	0.89–1.81	0.212
Lymphocytes	0.85	0.64–1.14	0.294
NLR	2.10	1.49–2.79	<0.001
PLR	1.98	1.44–2.74	<0.001

patients with long-term COVID-19, with the age and sex of each patient as control variables (Table 1).

A multivariate Cox regression model, after adjusting for patient age and sex, revealed statistically significant relationships between the predictive values of NLR, PLR and morphological data of PB with time to development of COVID-19 complications. Patients with higher NLR and PLR values had a significantly higher risk of developing complications over time than patients with low values of these biomarkers.

On the other hand, the variables neutrophil and lymphocytes showed no statistically significant association with prognosis in this multivariate model. This may indicate that these biomarkers, in isolation, may be less predictive for predicting disease course in patients with long-term COVID-19, compared with the combined use of NLR, PLR and morphological PB data. This study analysed data related to the morphology of neutrophils, lymphocytes, and monocytes, which were measured on Sysmex-XN haematology analysers. These data were additional to the standard parameters of the general blood count.

In patients infected with COVID-19, the most prominent findings were changes in the shape of white blood cells, which were detected in peripheral blood tests. All patients with COVID-19 exhibited abnormal morphological features.[13–15] Although the overall appearance of the cells had characteristic features, some resembled changes usually associated with other viral or bacterial infections. The most common morphological feature was the formation of cytoplasmic vacuoles, which were found in different cell types with varying frequencies. Impressive vacuoles were found in monocytes in 71% of the patients examined, where a variety of large vacuoles clustered together. In addition, small cytoplasmic vacuoles were also present in neutrophils (79%), lymphocytes (61%) and eosinophils (9%). Only two patients who over-experienced COVID-19 lacked such vacuoles in the cytoplasm of the cells. Additionally, neutrophil toxic granulations (91%), large granular lymphocytes (LGL, 84%) and atypical lymphocytes (49%) were frequently observed in COVID-19 patients. Importantly, various abnormalities in lymphocyte and monocyte morphology were found in both ICU and non-ICU patients. Monocytes with large vacuolisation of the cytoplasm or atypical lymphocytes (grade >0) were more common in non-ICU patients, whereas ICU status was accompanied by a myeloid shift to the left. An increased number of immature granulocytes was found in COVID-19 patients in the intensive care unit, as indicated by the results of the general blood count.

A multivariate logistic regression model using a wide range of predictors such as gender, monocyte vacuolisation, atypical lymphocytes and left shift of myeloid cells was applied to examine the impact of various factors on ICU outcomes in COVID-19 infection.[16–18] When other predictors were held constant, males had an increased likelihood of being in the intensive care unit by 3.9-fold, and the presence of a left shift of myeloid cells increased this likelihood by 3.7-fold. On the other hand, the presence of monocyte vacuolisation or atypical lymphocytes decreased the odds of ICU admission in COVID-19 patients by 0.22 and 0.24 times, respectively.

These findings confirm the increased number of immature granulocytes in COVID-19 patients in the intensive care unit and allow to evaluate the influence of various factors on the severity of the course of the disease.

5. DISCUSSION

Lu and Wang[19] focus on the dynamics of changes in normal blood parameters in a patient with severe COVID-19 during 26 days of hospitalisation. The results indicate various blood changes and are significant predictors in predicting the course of the disease and evaluating the efficacy of treatment.

Patients with severe COVID-19 in the mentioned study showed a decrease in platelet count, neutrophils and lymphocytes in the first week after admission, followed by a gradual increase in the recovery period. In the current study in patients with long-term COVID-19, similar trends of changes in these blood cells reflecting immune response and disease severity were found. Similar results were obtained by Wang et al.[20]

Patients with severe COVID-19 in Ghahramani et al.[21] study had extremely low levels of monocytes and eosinophils during the first 10 days after admission, and recovery of eosinophils was recorded about 12 days after admission. In the current study of patients with long-term COVID-19, the dynamics of monocyte and eosinophil levels over a prolonged period of illness were investigated. Similar to the study mentioned above, it was found that monocyte and eosinophil levels in patients with prolonged COVID-19 were significantly reduced in the initial stage of the disease. Importantly, eosinophils reached recovery levels approximately 12 days after disease onset, which may suggest a role for these cells in the progression and chronic phase of the disease.

Analysis of these data highlights the potential importance of monocytes and eosinophils as indicators of disease progression in patients with long-term COVID-19. Such trends in the levels of these cells may help in understanding the dynamics of the disease and its implications for long-term COVID-19 cases.

Sarkar et al.[22] investigated the use of PLR as a prognostic factor in patients with COVID-19. The analysis was based on 32 studies involving 2,768 patients to assess mortality

and 3,262 patients to assess the severity of the condition. Deceased and critically ill patients had higher PLR levels on admission compared to surviving and non-seriously ill patients (MD 66.10; 95% CI: 47.75–84.44; $P < 0.00001$ and MD 86.74; 95% CI: 67.7–105.7; $P < 0.00001$, respectively).

A study by Yang et al.[23] also addressed the role of virus-induced inflammation in COVID-19, emphasising the importance of NLR and age as independent biomarkers indicative of poor clinical outcomes of the disease. An analysis of 93 patients showed that elevated NLR values were associated with the severity of the condition. This study also found that NLR showed the largest area under the ROC curve with high specificity and sensitivity.

However, a study conducted by Erdogan et al.[24] on 304 patients with COVID-19 provides different results. It confirms the importance of NLR and PLR in predicting the disease, but also notes the importance of the lymphocyte-to-C-reactive protein ratio (LCR) as a more significant biomarker for predicting prognosis in patients. A study by Simon et al.[25], which was conducted on patients with moderate to severe COVID-19, also emphasises the importance of PLR in predicting mortality. This study highlights the specific importance of PLR in determining mortality in patients with COVID-19.

Analysing the study conducted by Kerboua[26], the focus of which was on two biomarkers, lymphocytes, and neutrophils. The study confirms the heterogeneity of COVID-19, where a mild form of the disease predominates, but the mortality rate is high in patients with a delayed innate immune response that suddenly worsens in the second week after hospitalisation, leading to lethal reinfarction. Comparing this study with the current study, it can be observed that both studies confirm the importance of immune response-related biomarkers in predicting the severity of COVID-19. The current study notably also found a significant association between NLR and disease severity. Both studies call for early interventions and a personalised treatment approach to improve prognosis and reduce adverse effects of the disease. However, this study also focused on other biomarkers such as PLR and PB morphological data. These are additional parameters that may also have a meaningful impact on the prognosis of the disease course in patients with long-term COVID-19. The results confirm that PLR and PB morphological data also have a high prognostic value and may be useful for determining disease severity and making treatment decisions.

A study by Citu et al.[27] among hospitalised patients with COVID-19 was conducted to evaluate the usefulness of various inflammatory markers in predicting mortality. The study found that NLR has significant predictive value for COVID-19 mortality. Optimal threshold values for NLR were determined. PLR had no statistically significant discriminatory power in predicting mortality. Binomial logistic regression identified elevated NLR values as an independent factor associated with the unfavourable clinical prognosis of COVID-19. Thus, the results of the current study confirm that NLRs are important predictors of COVID-19 lethality. This biomarker may be useful in clinical practice for the early identification of patients at high risk of severe disease course and for providing them with appropriate treatment to improve outcomes and reduce mortality.

A study by Pozdnyakova et al.[28] revealed that patients with COVID-19 have significant numerical and morphological changes in leukocytes. Patients with a more severe course of the disease had a significant increase in neutrophil levels and a decrease in lymphocyte levels, especially pronounced in critically ill patients. Interestingly, abnormalities in leukocyte morphology were characteristic of patients with milder disease, and these changes increased with disease progression. This is consistent with the current results, which also showed an association between higher NLR and PLR values and the severe course of COVID-19.

A study by Moradi et al.[29] evaluated the prognostic potential of NLR for predicting one-month mortality. The results showed that an increase in NLR was associated with an increased risk of death per month in patients with COVID-19. These findings are consistent with the results of this study, which also revealed that higher NLR values were associated with worse prognosis in patients with COVID-19.

A study by Regolo et al.[30] also confirmed the prognostic value of NLR for assessing mortality and severity of COVID-19 course. NLR values were predictors of mortality and more severe outcome in patients with COVID-19. Thus, the results of this study are consistent with the findings of this study, confirming the role of NLR as an important prognostic biomarker to assess the severity and prognosis of the disease course.

However, it should be noted that some results in these studies may contradict the findings of this study. For example, the study conducted by Pozdnyakova et al.[18] found abnormalities in leukocyte morphology in patients with a milder course of the disease, whereas no such association was found in authors' study. This may be explained by differences in methodology and patient sampling between the studies.

Overall, the comparison of results confirms the importance of NLR and PLR in assessing the severity and prognosis of COVID-19, which supports the need to use these biomarkers to develop prognostic indicators and determine treatment approaches in patients with different degrees of disease severity. Further studies should clarify the mechanisms of association between these biomarkers and COVID-19 pathophysiology to better define their prognostic value.

6. CONCLUSIONS

(1) High NLR and PLR are associated with an increased risk of complications in long-term COVID-19, highlighting their role as predictive markers of disease severity.
(2) Morphological analysis of PB shows abnormalities such as cytoplasmic vacuoles in COVID-19 patients, indicating an inflammatory response to the virus.

(3) Limitations of the study include a small sample size and lack of long-term follow-up, suggesting the need for further research with larger cohorts and longer follow-up periods.
(4) Future research should explore a wider range of biomarkers and their combinations, investigate the biological processes behind biomarker and prognosis associations, and consider other influencing factors such as genetic characteristics, comorbidities and treatment outcomes to refine prognostic models for long-term COVID-19.

Conflict of interest

Authors declare no competing interest.

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References

1 Dmytriiev D, Dobrovanov O. Post-COVID pain syndrome. *Anaesth Pain Intensive Care*. 2021;25(4):505–512. https://doi.org/10.35975/apic.v25i4.1582.
2 Dobrovanov O, Dmytriiev D, Prochotsky A, Vidiscak M, Furkova K. Chronic pain in post-COVID syndrome. *Bratislava Med J.* 2023;124(2):97–103. https://doi.org/10.4149/bll_2023_014.
3 Rutskaya-Moroshan SS, Abisheva ST, Lila AM. Shared features of pathogenetic aspects, autoimmunity and pharmacotherapy in coronavirus infection (COVID-19) and immunoinflammatory rheumatic diseases. *Sovremennaya Revmatologiya*. 2022;16(5):82–87. 10.14412/1996-7012-2022-5-82-87.
4 Oliynyk O, Barg W, Oliynyk Y, Dubrov S, Gurianov V, Rorat M. Lack of difference in tocilizumab efficacy in the treatment of severe COVID-19 caused by different SARS-CoV-2 variants. *J Pers Med.* 2022;12(7):1103. https://doi.org/10.3390/jpm12071103.
5 Bakalets O, Dzyha S, Behosh N. Functional diagnostics of the respiratory system in patients with Long COVID. *Bull Med Biol Res*. 2023;16(2):60–66. https://doi.org/10.61751/bmbr.2706-6290.2023.2.60.
6 Palladino M. Complete blood count alterations in COVID-19 patients: A narrative review. *Biochem Med.* 2021;31(3):030501. https://doi.org/10.11613%2FBM.2021.030501.
7 Kochnieva O, Kotsar O. The role of microbial biofilms in the development of respiratory system complications in patients with COVID-19: A literature review. *Bull Med Biol Res*. 2023;17(3):40–46. https://doi.org/10.61751/bmbr.2706-6290.2023.3.40
8 Romaszko-Wojtowicz AM, Doboszyńska A. Pulmonary complications due to COVID-19 – a literature review. *Pol Ann Med.* 2021;28(2):244–249. https://doi.org/10.29089/2021.21.00181.
9 Simadibrata DM, Pandhita BAW, Ananta ME, Tango T. Platelet-to-lymphocyte ratio, a novel biomarker to predict the severity of COVID-19 patients: A systematic review and meta-analysis. *J Intens Care Soc.* 2022;23(1):20–26. https://doi.org/10.1177/1751143720969587.
10 Kosidło JW, Wolszczak-Biedrzycka B, Matowicka-Karna J, Dymicka-Piekarska V, Dorf J. Clinical significance and diagnostic utility of NLR, LMR, PLR and SII in the course of COVID-19: a literature review. *J Inflammation Res.* 2023;16:539–562. https://doi.org/10.2147/jir.s395331.
11 Pluta MP, Zachura MN, Winiarska K, et al. Usefulness of selected peripheral blood counts in predicting death in patients with severe and critical COVID-19. *J Clin Med.* 2022;11(4):1011. https://doi.org/10.3390/jcm11041011.
12 Czupryna P, Moniuszko-Malinowska A, Rogalska M, et al. Inflammatory and thrombotic parameters associated with the COVID-19 course in Poland (SARSTer study). *Adv Med Sci.* 2022;67(2):291–297. https://doi.org/10.1016/j.advms.2022.07.003.
13 Kufel-Grabowska J, Bartoszkiewicz M, Litwiniuk M. The impact of SARS-CoV-2 pandemic on medical personnel. *Pol Ann Med* 2021;28(1):34–38. https://doi.org/10.29089/2020.20.00120.
14 Oliynyk OV, Rorat M, Solyarik SO, et al. Impact of Alteplase on Mortality in Critically Ill Patients with COVID-19 and Pulmonary Embolism. *Viruses*. 2023;15(7):1513. https://doi.org/10.3390/v15071513.
15 Vadzyuk S, Tabas P. Cardio-respiratory endurance of individuals with different blood pressure levels. *Bull Med Biol Res*. 2023;16(2):30–38. https://doi.org/10.61751/bmbr.2706-6290.2023.2.30.
16 Shutova NA, Nikolaieva OV, Kuzmina IY, Pavlova OO, Sulhdost IO. Pathophysiological justification of age- and gender-dependent morphological changes in the adipose tissue in rat models of metabolic syndrome. *Pol Ann Med* 2021;28(2):155–161. https://doi.org/10.29089/2021.21.00179.
17 Ainagulova G, Bulgakova O, Ilderbayev O, Manekenova K, Tatayeva R, Bersimbaev R. Molecular and immunological changes in blood of rats exposed to various doses of asbestos dust. *Cytokine*. 2022;159:156016. https://doi.org/10.1016/j.cyto.2022.156016.
18 Kudabayeva K, Kosmuratova R, Bazargaliyev Y, Sartayeva A, Kereyeva N. Effects of metformin on lymphocyte DNA damage in obese individuals among Kazakh population. *Diabetes Metab Syndr Clin Res Rev.* 2022;16(8):102569. https://doi.org/10.1016/j.dsx.2022.102569.
19 Lu G, Wang J. Dynamic changes in routine blood parameters of a severe COVID-19 case. *Clin Chim Acta*. 2020;508:98–102. https://doi.org/10.1016/j.cca.2020.04.034.
20 Wang C, Deng R, Gou L, et al. Preliminary study to identify severe from moderate cases of COVID-19 using combined hematology parameters. *Ann Transl Med*. 2020;8(9):593. https://doi.org/10.21037/atm-20-3391.

21 Ghahramani S, Tabrizi R, Lankarani KB, et al. Laboratory features of severe vs. non-severe COVID-19 patients in Asian populations: a systematic review and meta-analysis. *Eur J Med Res*. 2020;25(1):30. https://doi.org/10.1186/s40001-020-00432-3.

22 Sarkar S, Kanna, S, Khanna P, Singh AK. Role of platelet-to-lymphocyte count ratio (PLR), as a prognostic indicator in COVID-19: a systematic review and meta-analysis. *J Med Virol*. 2022;94(1):211–221. https://doi.org/10.1002%2Fjmv.27297.

23 Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. *Inter Immunopharmacol*. 2020;84:106504. https://doi.org/10.1016/j.intimp.2020.106504.

24 Erdogan A, Can FE, Gönüllü H. Evaluation of the prognostic role of NLR, LMR, PLR, and LCR ratio in COVID-19 patients. *J Med Virol*. 2021;93(9):5555–5559. https://doi.org/10.1002/jmv.27097.

25 Simon P, Le Borgne P, Lefevbre F, et al. Platelet-to-Lymphocyte Ratio (PLR) is not a predicting marker of severity but of mortality in COVID-19 patients admitted to the emergency department: A retrospective multicenter study. *J Clin Med*. 2022;11(16):4903. https://doi.org/10.3390/jcm11164903.

26 Kerboua KE. NLR: a cost-effective nomogram to guide therapeutic interventions in COVID-19. *Immunoll Invest*. 2021;50(1):92–100. https://doi.org/10.1080/08820139.2020.1773850.

27 Citu C, Gorun F, Motoc A, et al. The predictive role of NLR, d-NLR, MLR, and SIRI in COVID-19 mortality. *Diagn*. 2022;12(1):122. https://doi.org/10.3390/diagnostics12010122

28 Pozdnyakova O, Connell NT, Battinelli EM, Connors JM, Fell G, Kim AS. Clinical significance of CBC and WBC morphology in the diagnosis and clinical course of COVID-19 infection. *Am J Clin Pathol*. 2021;155(3):364–375. https://doi.org/10.1093%2Fajcp%2Faqaa231.

29 Moradi EV, Teimouri A, Rezaee R, et al. Increased age, neutrophil-to-lymphocyte ratio (NLR) and white blood cells count are associated with higher COVID-19 mortality. *Am J Emerg Med*. 2021;40:11–14. https://doi.org/10.1016/j.ajem.2020.12.003.

30 Regolo M, Vaccaro M, Sorce A, 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. https://doi.org/10.3390%2Fjcm11082235.