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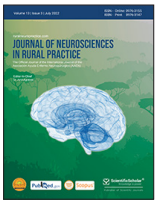
Journal of Neurosciences in Rural Practice

Article in Press



*Original Article*

# Associations of the neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio, and platelet/lymphocyte ratio with COVID-19 disease severity in patients with neurological symptoms: A cross-sectional monocentric study

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## ABSTRACT

**Objectives:** Data are limited regarding the relationship of neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), and platelet/lymphocyte ratio (PLR) with neurological symptoms (NS) in COVID-19 patients. This study is the first to assess the utility of the NLR, MLR, and PLR for predicting COVID-19 severity in infected patients with NS.

**Materials and Methods:** Consecutive 192 PCR-positive COVID-19 patients with NS were included in this cross-sectional and prospective study. The patients were classified into the non-severe and severe groups. We analyzed routinely complete blood count in these groups in terms of COVID-19 disease severity.

**Results:** Advanced age, a higher body mass index, and comorbidities were significantly more common in the severe group ($P < 0.001$). Among the NS, anosmia ($P = 0.001$) and memory loss ($P = 0.041$) were significantly more common in the non-severe group. In the severe group, the lymphocytes and monocyte counts and the hemoglobin level were significantly lower, while the neutrophil count, NLR, and PLR were significantly higher (all $P < 0.001$). In the multivariate model, advanced age and a higher neutrophil count were independently associated with severe disease (both $P < 0.001$) but the NLR and PLR were not (both $P > 0.05$).

**Conclusion:** We found positive associations of COVID-19 severity with the NLR and PLR in infected patients with NS. Further research is required to shed more light on the role of neurological involvement in disease prognosis and outcomes.

**Keywords:** COVID-19, Monocyte to lymphocyte ratio, Neurological symptoms, Neutrophil to lymphocyte ratio, Platelet to lymphocyte ratio

## INTRODUCTION

The COVID-19 pandemic began at the end of 2019; the disease typically affects the respiratory system but is also associated with multiorgan dysfunction that can involve the central and peripheral nervous systems.[1-3] This was evident even during the early stage of the pandemic.[1,4] The central nervous system (CNS) can be invaded through the bloodstream or retrograde neuronal route. Virus in the blood first infects endothelial cells of the blood-brain barrier or choroid plexus epithelial cells of the blood-cerebrospinal fluid barrier or reaches the CNS in leukocytes. Slow blood flow in the capillary endothelium of the brain microcirculatory system increases viral interaction with the angiotensin-converting enzyme 2 (ACE2) receptor, thus facilitating viral entry into the CNS after capillary endothelial damage.[5,6] Alternatively, the virus may directly infect peripheral olfactory sensory neurons and then progress to the cranial nerves through retrograde axonal transport.[7] Finally, neurons may be indirectly affected by increased cytokine levels attributable to widespread inflammation, an immune response, or hypoxia.[8]

Inflammation triggered by the immune response plays an important role in the progress of infection.[9] When an immune response is activated, the neutrophil and leukocyte counts, neutrophil/lymphocyte ratio (NLR), and monocyte/lymphocyte ratio (MLR) increase; the platelet/lymphocyte ratio (PLR) decreases in severe cases.[10-15] Few studies have examined the association between these routine complete blood count (CBC) parameters and the development of neurological disease. Flores-Silva *et al.* reported significantly lower hemoglobin and lymphocyte levels, and significantly higher total neutrophil counts, in COVID-19 patients with

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**Received:** 07 September 2022 **Accepted:** 08 September 2022 **EPub Ahead of Print:** 22 October 2022 **Published:** XXXXXX **DOI:** 10.25259/JNRP_6_2022

neurological findings.[16] In another study, low hemoglobin and platelet levels were associated with COVID-19-related headache, and an increased NLR and decreased platelet count were independent predictors of headache.[17] This study is the first to assess the utility of the NLR, MLR, and PLR for predicting COVID-19 severity in infected patients with neurological symptoms (NS).

## MATERIALS AND METHODS

### Study population

We enrolled 192 PCR-positive COVID-19 patients with NS treated as outpatients in our pandemic clinic, or hospitalized between January and June 2021. Patients aged <18 years, those with chronic kidney, heart, liver, or malignant disease, and those who were pregnant or morbidly obese were excluded from the study. The study began only after approval from the ethics committee of Kirsehir Ahi Evran University Faculty of Medicine (approval date January 05, 2021; approval no. 2021-01/04). We prospectively collected demographic data, and noted any comorbid diseases or COVID-19-related NS (ageusia and anosmia, dizziness, headache, cranial neuropathy, memory loss, stroke, epilepsy, myopathy, and neuropathic pain). Patients reporting memory loss were evaluated using the Montreal Cognitive Assessment and those with cranial neuropathy, dizziness, epileptic seizures, or stroke underwent detailed neurological examination and cranial tomography. The complaints of the other patients were also noted. Patients were divided into mild, moderate, severe, and critical illness groups. Mild disease was defined as an absence of respiratory symptoms and pulmonary radiological signs, and oxygen saturation ($SpO_2$) ≥96%; moderate disease was defined as the presence of mild respiratory symptoms, radiological evidence of pneumonia, and 93%< $SpO_2$ <96%; severe disease was defined as $SpO_2$ ≤93% requiring oxygen support; and critical disease was defined as a need for intensive care.[18] The patients were then divided into severe and non-severe disease groups, which subsumed critically and severely ill patients, and those with mild and moderate disease, respectively.

### Data collection

Blood samples were collected on admission or the 1st day of hospitalization. CBCs were obtained with the LH 750 autoanalyzer (Beckman Coulter, Fullerton, CA, USA). The hemoglobin level, red cell width distribution, white blood cell (WBC), neutrophil, lymphocyte, monocyte, and platelet counts, mean platelet volume, platelet distribution width, and plateletcrit were recorded. The NLR, MLR, and PLR were calculated.

### Statistical analysis

All statistical analyses were performed using SPSS for Windows software (version 25.0; IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov and Shapiro–Wilks tests were used to verify that the quantitative data were normally distributed. Kurtosis and skewness coefficients were calculated. Data are presented as mean ± standard deviation, median (25–75th percentile), or number (%). The Chi-squared test, Fisher's exact test, Fisher-Freeman-Halton exact test, and independent t-test were used as appropriate for univariate analyses. Nonnormally distributed variables were compared using the Mann–Whitney U test. To identify risk factors for severe disease, we initially performed univariate logistic regression. Significant variables were included in the multivariate logistic regression analysis. $P < 0.05$ was considered significant.

## RESULTS

Of the 192 patients, 76 and 116 were classified into the non-severe and severe groups, respectively. The results of group comparisons are shown in [Table 1]. Advanced age, a higher body mass index (BMI), and comorbidities were significantly more common in the severe group ($P < 0.001$). Among the comorbidities, diabetes mellitus ($P < 0.001$), hypertension ($P < 0.001$), coronary artery disease ($P = 0.039$), and chronic obstructive pulmonary disease ($P = 0.040$) were significantly more prevalent in the severe group. Among the NS, anosmia ($P = 0.001$) and memory loss ($P = 0.041$) were significantly more common in the non-severe group. We found no significant association between the number of NS and disease severity ($P = 0.100$). In the severe group, the lymphocytes and monocyte counts and the hemoglobin level were significantly lower, while the neutrophil count, NLR, and PLR were significantly higher (all $P < 0.001$).

The results of the regression analysis are shown in [Table 2]. In univariate analysis, advanced age, higher BMI, comorbid conditions, anosmia higher neutrophil count, lower lymphocyte and monocyte counts, and higher NLR and PLR were significantly associated with severe disease (all $P < 0.001$). A 1-unit increase in the NLR and PLR increased the risk of severe disease 1.175- and 1.006-fold, respectively, (both $P < 0.001$). In the multivariate model, advanced age and a higher neutrophil count were independently associated with severe disease (both $P < 0.001$) but the NLR and PLR were not (both $P > 0.05$).

## DISCUSSION

In this study, advanced age, a higher BMI, and comorbidities were significantly more common in the severe group; anosmia and memory loss were significantly more prevalent in the non-severe group; the lymphocyte and monocyte counts and the hemoglobin level were significantly lower, while the neutrophil count, NLR, and PLR were significantly higher, in the severe group; and advanced age and a higher

**Table 1:** Demographic and laboratory data (*n*=192).

| Variables | Non-severe group (*n*=116) % | Severe group (*n*=76) | *P* | Effect size |
|---|---|---|---|---|
| Age (years) | 37.06±10.72 | 56.32±11.28 | **0.000** | −1.758 |
| Body mass index (kg/m$^2$) | 26.38±4.74 | 29.06±4.65 | **0.000** | −0.570 |
| Female gender | 67 (57.8) | 42 (%55.3) | 0.733 | 0.025 |
| Comorbidities | 30 (25.9) | 45 (61.6) | **0.000** | 0.356 |
| Diabetes mellitus | 6 (5.2) | 24 (32.9) | **0.000** | 0.369 |
| Hypertension | 8 (6.9) | 22 (30.1) | **0.000** | 0.310 |
| Coronary artery disease | 7 (6.0) | 11 (15.1) | **0.039** | 0.150 |
| Chronic obstructive pulmonary disease | 6 (5.2) | 10 (13.7) | **0.040** | 0.149 |
| Neurological symptoms | | | | |
| Ageusia | 72 (62.1) | 37 (48.7) | 0.067 | 0.132 |
| Anosmia | 71 (61.2) | 28 (36.8) | **0.001** | 0.238 |
| Dizziness | 14 (12.1) | 15 (19.7) | 0.147 | 0.105 |
| Headache | 93 (80.2) | 61 (80.3) | 0.988 | 0.001 |
| Cranial neuropathy | 2 (1.7) | 1 (1.3) | 0.823 | 0.016 |
| Memory loss | 17 (14.7) | 4 (5.3) | **0.041** | 0.147 |
| Stroke | 0 (0.0) | 1 (1.3) | 0.396 | 0.089 |
| Epilepsy | 0 (0.0) | 1 (1.3) | 0.396 | 0.089 |
| Myopathy | 0 (0.0) | 1 (1.3) | 0.396 | 0.089 |
| Neuropathic pain | 2 (1.7) | 6 (7.9) | 0.060 | 0.151 |
| Complete blood count | | | | |
| White blood cell (10$^3$/mm$^3$) | 6.39 (4.60–7.60) | 6.46 (4.70–9.18) | 0.577 | −0.249 |
| Neutrophil | 3.88±1.86 | 5.44±3.36 | **0.000** | −0.609 |
| Lymphocyte | 1.67±0.81 | 1.10±0.65 | **0.000** | 0.753 |
| Monocyte | 0.62±0.29 | 0.42±0.24 | **0.000** | 0.711 |
| Hemoglobin (mg/dL) | 14.05±1.69 | 13.07±1.64 | **0.000** | 0.584 |
| Platelet (10$^3$/mm$^3$) | 226.0 (192.25–261.75) | 226.5 (169.0–294.0) | 0.767 | −0.075 |
| RDW (%) | 12.8 (12.3–13.4) | 13.1 (12.5–13.7) | 0.121 | -0.105 |
| MPV (fL) | 10.38±0.92 | 10.29±0.92 | 0.497 | 0.100 |
| PCT (%) | 0.23 (0.21–0.27) | 0.23 (0.18–0.28) | 0.515 | 0.003 |
| PDW (fL) | 11.9 (10.8–13.1) | 11.4 (10.1–12.8) | 0.087 | 0.214 |
| NLR | 2.25 (1.51–3.17) | 4.86 (2.40–8.84) | **0.000** | 0.462 |
| MLR | 0.31 (0.22–0.60) | 0.37 (0.28–0.52) | 0.509 | 0.056 |
| PLR | 148.8 (111.8–208.6) | 233.5 (141.8–331.8) | **0.000** | 0.410 |

*P*<0.05 are considered significant and given as bold

neutrophil count were independent predictors of COVID-19 severity, whereas the NLR and PLR were not.

COVID-19 can have direct and indirect neurological effects. In the former case, the virus achieves "retrograde neuronal access" through the peripheral nerves, spreads hematogenously by directly infecting endothelial cells, and then infiltrates other infected cells. Indirect virus exposure is reflected in marked increases in inflammatory cytokines, hypoxia, and systemic inflammation.[8] Headache, anosmia, ageusia, fatigue, dizziness, and memory loss were the most common NS as in our patients.[19] Anosmia and ageusia were significantly more common in the non-severe group, suggesting that the virus travelled from the nasal cavity to the brain through the cranial nerves.[20] The anosmia and ageusia rates were 19.4–88% in COVID-19-infected patients, who had good prognoses.[21,22] Lechien *et al.* reported that the olfactory neuroepithelium and bulb limited viral spread, thereby improving prognosis despite local irritation.[21] In this study, anosmia was significantly more common in the non-severe group, as was memory loss. This may be explained by the fact that we did not evaluate intensive care patients, who would be expected to show more cognitive effects. Although the symptoms were not confirmed by neuropsychiatric testing, no patient reported memory loss before infection. The pathophysiology of cognitive impairment remains unclear. The virus may directly affect the brain, or the effects may be non-specific (due to medical intervention, systemic inflammation, assisted ventilation, psychosocial tension,[8] quarantine, etc.). Anxiety, depression, and other mental health problems caused by a lack of social interaction negatively affect cognitive function, and a vicious cycle may develop.[23]

Obesity is an independent risk factor for the lower respiratory tract infection and mortality (due to severe tissue damage) in COVID-19-infected patients.[24] First, organ damage caused by obesity leads to metabolic syndrome; stress then

**Table 2:** Univariate and multiple logistic regression analyses to identify the predictors of COVID-19 severity in patients with neurological symptoms.

| Variables | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95% CI) | *P* | OR (95% CI) | *P* |
| Age (years) | 1.157 (1.112–1.204) | **0.000** | 1.284 (1.154–1.429) | **0.000** |
| Body mass index (kg/m$^2$) | 1.127 (1.056–1.204) | **0.000** | 1.170 (1.002–1.370) | 0.051 |
| Female gender | 1.107 (0.618–1.983) | 0.733 | - | - |
| Comorbidities | 4.607 (2.457–8.639) | **0.000** | 1.841 (0.292–11.622) | 0.516 |
| Neurological symptoms | | | | |
| Ageusia | 1.725 (0.960–3.098) | 0.068 | - | - |
| Anosmia | 0.705 (1.489–4.915) | **0.001** | 2.561 (0.539–12.163) | 0.237 |
| Dizziness | 1.792 (0.809–3.965) | 0.150 | - | - |
| Headache | 1.006 (0.487–2.079) | 0.988 | - | - |
| Cranial neuropathy | 1.316 (0.117–14.769) | 0.824 | - | - |
| Memory loss | 3.091 (0.998–9.575) | 0.051 | - | - |
| Neuropathic pain | 4.886 (0.959–24.880) | 0.056 | - | - |
| Complete blood count | | | | |
| White blood cell ($10^3$/mm$^3$) | 1.091 (0.985–1.208) | 0.095 | - | - |
| Neutrophil | 1.266 (1.117–1.434) | **0.000** | 2.152 (1.436–3.226) | **0.000** |
| Lymphocyte | 0.307 (0.185–0.510) | **0.000** | 1.423 (0.611–3.315) | 0.237 |
| Monocyte | 0.053 (0.014–0.202) | **0.000** | 25.490 (1.170–555.30) | 0.039 |
| Hemoglobin (mg/dL) | 0.705 (0.585–1.850) | 0.067 | - | - |
| Platelet ($10^3$/mm$^3$) | 1.001 (0.997–1.004) | 0.609 | - | - |
| RDW (%) | 1.089 (0.860–1.379) | 0.478 | - | - |
| MPV (fL) | 0.895 (0.652–1.230) | 0.495 | - | - |
| PCT (%) | 0.964 (0.021–45.096) | 0.985 | - | - |
| PDW (fL) | 0.898 (0.776–1.040) | 0.152 | - | - |
| NLR | 1.175 (1.076–1.283) | **0.000** | 1.011 (0.827–1.237) | 0.913 |
| MLR | 1.104 (0.866–1.406) | 0.425 | - | - |
| PLR | 1.006 (1.003–1.009) | **0.000** | 1.000 (0.996–1.003) | 0.898 |

NLR: Neutrophil/lymphocyte ratio, MLR: Monocyte/lymphocyte ratio, PLR: Platelet/lymphocyte ratio. $P<0.05$ are considered significant and given as bold

exacerbates the associated dysfunction. Second, the virus can invade adipose tissue, which increases the vulnerability of the heart and lungs (which express the viral ACE2 receptor). Third, obesity is associated with the high levels of inflammation and an elevated immune response, potentially leading to burnout. Obesity increases abdominal pressure, restricts chest expansion, and renders lung compensation inadequate; obese patients are at increased risk of respiratory failure.[25] A high BMI (>28 kg/m$^2$) and diabetes mellitus are risk factors for severe COVID-19 disease.[26] Several studies reported increased COVID-19-related mortality in hypertensive and older patients.[27,28] Bastug *et al.* found that intensive care unit patients were older and had more comorbidities than other patients (76.1 vs. 33.1%).[11] The mean age of our severely ill group was 56.32 ± 11.28 years, which was significantly higher than that of the non-severe group (37.06 ± 10.72 years). The oxidant effects of aging and obesity, as well as chronic diseases such as diabetes, increase the severity of COVID-19 disease.[29]

Blood parameters have been extensively studied in patients with severe and non-severe COVID-19 infections; an increased neutrophil count, C-reactive protein (CRP) level and NLR, and a decreased lymphocyte count were indicators of inflammation.[10,30,31] The CRP level is commonly elevated in patients with severe disease, as well as in some mild cases. The CRP level is a marker of infection, but not of COVID-19 disease severity.[31] Lymphocytopenia reflects strong immune system activation even in the early stages of COVID-19 infection and is associated with a poor prognosis.[32] A recent review showed that lymphocytopenia is a component of the cytokine storm associated with severe COVID-19 infection, along with an elevated WBC count and IL-6 level.[31,33-35] In particular, a high NLR was an independent prognostic factor for COVID-19 outcomes and marker of clinical severity.[36] In a Turkish study, the lymphocyte count and hemoglobin level were low, while the leukocyte and neutrophil counts, and NLR, MLR, and PLR were high in critically ill patients transferred to intensive care units.[11] Few studies have evaluated CBC parameters in COVID-19 patients with NS.[16,17] In Mexico City, a high NLR (≥9) in hospitalized patients was an independent predictor of the development of in-hospital neurological complications; the hemoglobin level and lymphocyte count were significantly lower, while the total neutrophil count was significantly higher, in these patients.[16] Hussein *et al.* found that a low

hemoglobin level and platelet count were associated with COVID-19-related headache; an increased NLR and decreased platelet count were independent predictors of headache.[17] Wijeratne *et al*. noted an increased NLR in a 75-year-old male who developed acute stroke-like symptoms and signs during the course of COVID-19 disease.[37] We also found that the neutrophil count, NLR, and PLR were significantly higher, while the lymphocyte count was lower, in severely ill patients with NS. Elevated NLR and PLR are partly attributable to a low lymphocyte count. However, this does not fully explain the increased NLR; the neutrophil count increase was significant in our patients, even in multivariate analysis. In univariate analysis, a 1-unit increase in the NLR and PLR increased the risk of severe disease 1.175- and 1.006-fold, respectively. However, these increases were not significant in multivariate, possibly due to the small sample size. The hemoglobin level was low in the severe group, as previously reported.[17] As blood samples were collected on admission or the 1st day of hospitalization, this may reflect pre-existing anemia caused by chronic hypertension and/or other comorbidities, rather than COVID-19.

This study had some limitations. First, it was a relatively small single-center study. Second, a cross-sectional design was used so causality cannot be inferred. Furthermore, we measured laboratory parameters only once; obtaining more measurements in a longitudinal study might aid prediction of COVID-19 severity. Third, we lacked data on inflammatory markers (such as interleukins). Fourth, neither magnetic resonance imaging nor electrophysiological tests were performed because infection control measures were in place.

## CONCLUSION

Similar to prior reports, we found positive associations of COVID-19 severity with the NLR and PLR in infected patients with NS. Although these markers are not ideal, they are readily available and may assist the identification of patients at increased risk of severe COVID-19. Further longitudinal studies including larger cohorts are needed to shed more light on the role of neurological involvement in disease prognosis and outcomes.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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**How to cite this article:** Sahin BE, Celikbilek A, Kocak Y, Koysuren A, Hizmali1 L. Associations of the neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio, and platelet/lymphocyte ratio with COVID-19 disease severity in patients with neurological symptoms: A cross-sectional monocentric study. J Neurosci Rural Pract, doi: 10.25259/JNRP_6_2022