

# A High Neutrophil-Lymphocyte Ratio Is Associated With Increased Morbidity and Mortality in Patients With Coronavirus Disease 2019

**OBJECTIVES:** The neutrophil-lymphocyte ratio is an inexpensive and simple inflammatory marker. A higher ratio, indicative of an acute hyperinflammatory response or diminished overall physiologic health status, has been associated with poor prognoses. This study aimed to evaluate the prognostic potential of admission neutrophil-lymphocyte ratio in patients admitted to the medical ICU with coronavirus disease 2019.

**DESIGN:** Retrospective review of prospectively collected data.

**SETTING:** Medical ICU from a large medical center.

**PATIENTS:** 2,071 consecutive patients admitted to the medical ICU with laboratory-confirmed severe acute respiratory syndrome coronavirus-2 between March 15, 2020, and December 30, 2020, were grouped by neutrophil-lymphocyte ratio above or below the median (7.45) at the time of hospital admission.

**INTERVENTIONS:** Complete blood count with differential at the time of hospital admission.

**MEASUREMENTS AND MAIN RESULTS:** A neutrophil-lymphocyte ratio above 7.45 at the time of hospital admission was associated with increased need for mechanical ventilation (45.8% vs 38.0%,  $p < 0.0001$ ), vasopressor therapy (55.6% vs 48.2%,  $p = 0.001$ ), and decreased survival through 180 days (54.8% vs 67.0%,  $p < 0.0001$ ). Patients with a high neutrophil-lymphocyte ratio exhibited a 1.32 (95% CI, 1.14–1.54) times greater risk of mortality than those with a low neutrophil-lymphocyte ratio.

**CONCLUSIONS:** The neutrophil-lymphocyte ratio at the time of hospital admission is an independent risk factor for morbidity and mortality. This prognostic indicator may assist clinicians appropriately identify patients at heightened risk for a severe disease course and tailor treatment accordingly.

**KEY WORDS:** coronavirus disease 2019; intensive care; lymphocyte; neutrophil; neutrophil-lymphocyte ratio

Coronavirus disease 2019 (COVID-19) has caused significant morbidity and mortality worldwide (1). The variety in disease course presents challenges in patient triage and management. To date, there are limited data on a prognostic indicator of outcome after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

The human response to viral infections relies upon cytotoxic lymphocytes, such as T lymphocytes and natural killer cells (2). Patients with low baseline numbers of lymphocytes can exhaust antiviral immunity at an early stage, resulting in disease progression and poor outcomes (2). The neutrophil-lymphocyte ratio (NLR), accounting for relative amounts of neutrophils

Alexander H. King, MS<sup>1</sup>

Omar Mehkri, MD<sup>1</sup>

Prabalini Rajendram, MD<sup>1</sup>

Xiaofeng Wang, PhD<sup>2</sup>

Vidula Vachharajani, MD<sup>1</sup>

Abhijit Duggal, MD<sup>1</sup>

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and lymphocytes, has been studied in many disease processes (3–6). A higher ratio, reflective of either increased neutrophils (acute hyperinflammatory response) or decreased lymphocytes (decreased expansion and/or increased apoptosis), has been associated with poor prognoses (7–9).

Identification of accurate biomarkers for disease progression and outcome in COVID-19 can allow clinicians to identify patients for early aggressive management. The objective of this study was to evaluate the prognostic potential of NLR in patients admitted with COVID-19.

## MATERIALS AND METHODS

A single-center, multisite registry of prospectively collected data was retrospectively reviewed to analyze all patients admitted to the medical ICU (MICU) with laboratory-confirmed COVID-19 infection and a complete blood count with differential (CBC-Diff) between March 15, 2020, and December 30, 2020. This study was approved by the Cleveland Clinic Foundation institutional review board (Study 20-404). Patients were included if they had a positive polymerase-chain-reaction assay for SARS-CoV-2 and a CBC-Diff within 24 hours of hospital admission.

The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count (ALC) of the baseline CBC-Diff. Patients were separated into two cohorts based on whether they were above or below the median NLR of 7.45. Patients were followed using phone calls and visits in the electronic medical record, a statewide compendium of inpatient and outpatient records, and publically available obituaries by name and date of birth for patients at risk.

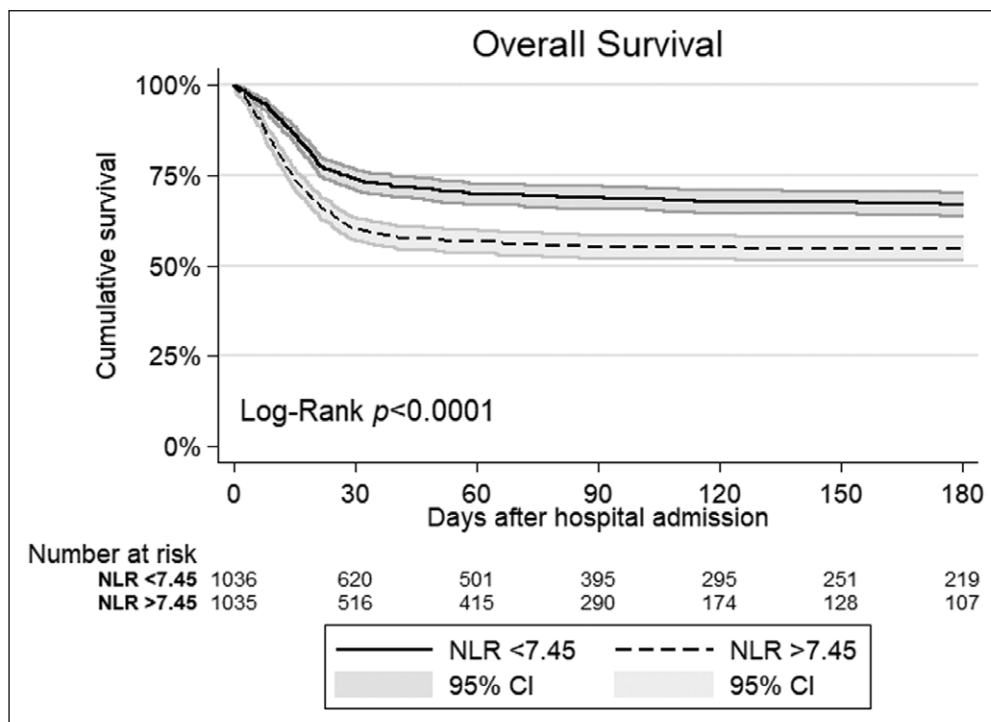
The primary outcome was 180-day survival from the day of hospital admission. Only patients who were discharged alive were used in the hospital and ICU length of stay (LOS) calculations. Secondary outcomes included the requirement of organ support measures including mechanical ventilation and vasopressor therapy. Kaplan-Meier survival analysis was used to assess 180-day survival with censoring of patients at last available follow-up. Multivariable analysis was performed using the Cox proportional hazards model with backward elimination where variables with  $p > 0.20$  were removed in a stepwise fashion. All baseline comorbid factors including severity of illness,

requirements for vasopressor therapy, and intubation were included in the initial model. All analyses were performed using Stata version 16.1 (Stata Corporation, College Station, TX).

## RESULTS

Of the 2,125 patients admitted to the MICU with COVID-19, 2,071 (97.6%) had a CBC-Diff upon hospital admission at a mean of 4.3 hours from the time of admission. Across the study population, the median NLR was 7.45 (interquartile range, 4.31–13.64). The high NLR group were older ( $69.0 \pm 14.0$  vs  $65.5 \pm 15.7$ ,  $p < 0.0001$ ), more often White (66.9% vs 52.6%,  $p < 0.0001$ ). The distribution of comorbidities between the groups had slight differences. Patients with a high baseline NLR had increased Acute Physiology and Chronic Health Evaluation (APACHE) III scores ( $62.8 \pm 27.0$  vs  $54.8 \pm 26.3$ ,  $p < 0.001$ ), more frequently had chronic kidney disease (43.6% vs 37.6%,  $p = 0.006$ ) and cancer (45.0% vs 37.3%,  $p < 0.001$ ), but less often had diabetes (57.8% vs 63.2%,  $p = 0.01$ ). The remaining baseline characteristics were similar between the groups. There were some temporal differences in the prevalence of high versus low NLR throughout the time course of this study. In Q1 (January to March) and Q2 (April to June) 2020, there were more patients presenting with a low NLR (61.7% vs 38.3%,  $p = 0.02$ ; 62.0% vs 38.0%,  $p < 0.001$ , respectively). Q3 (July to September) had similar rates of high and low NLRs ( $p = 0.22$ ), whereas Q4 (October to December) reversed trend with a greater amount of patients with high NLR (56.4% vs 43.6%,  $p < 0.001$ ). Pharmacologic therapy was broadly similar in both cohorts, with a few differences likely attributing to the differences in month of hospital admission. Patients with high NLR more often received antibiotics (93.7% vs 86.4%,  $p < 0.001$ ), dexamethasone (74.4% vs 61.7%,  $p < 0.001$ ), and less often received hydroxychloroquine (6.0% vs 11.6%,  $p < 0.001$ ).

Overall, the crude rate of all-cause mortality through 180 days was 34.2%. In the high NLR group, 419 patients (40.5%) died compared with 289 (27.9%) in the low NLR group. Kaplan-Meier estimates of survival were significantly greater in the low NLR cohort at 30 days (73.9% vs 60.2%), 60 days (69.8% vs 56.7%), and 180 days (67.0% vs 54.8%) ( $p < 0.0001$ ) (**Fig. 1**). On univariate analysis, the high NLR cohort had 1.63 (95%



**Figure 1.** Kaplan-Meier survival analysis of patients with low versus high neutrophil-lymphocyte ratio (NLR).

CI, 1.40–1.89;  $p < 0.001$ ) times the risk of death compared with the low NLR group. The corresponding risk was 1.32 (95% CI, 1.14–1.54) on multivariable analysis.

**Supplemental Table 1** (<http://links.lww.com/CCX/A648>) illustrates factors associated with 180-day mortality. On multivariable analysis, age, vasopressor use, NLR greater than 7.45, intubation, and increased APACHE III scores at baseline were independently associated with mortality. Across the three waves of COVID-19 admissions, there was consistency among factors associated with mortality.

Patients with high NLR more often received mechanical ventilation (45.8% vs 38.0%,  $p < 0.001$ ) with no differences in duration ( $10.1 \pm 9.0$  vs  $10.6 \pm 9.7$  d,  $p = 0.40$ ). High NLR was also associated with more frequent need for vasopressors (55.6% vs 48.2%,  $p = 0.001$ ). Greater hospital LOS ( $14.6 \pm 10.9$  vs  $12.6 \pm 10.1$ ,  $p = 0.0004$ ) and ICU ( $6.8 \pm 7.2$  vs  $5.9 \pm 7.8$ ,  $p = 0.03$ ) LOS were also associated with elevated NLR.

Since the NLR at the time of hospital admission was used, a subgroup analysis of 1,411 patients (68.1%) admitted to the ICU within 24 hours of hospital admission, including patients with direct admissions to the ICU, was performed. In this cohort, the same findings persisted with increased rates of mechanical

ventilation (46.1% vs 35.5%,  $p < 0.001$ ), vasopressor use (55.3% vs 44.3%,  $p < 0.001$ ), and mortality through 180 days (43.0% vs 26.6%,  $p < 0.001$ ).

## DISCUSSION

This study shows that NLR may serve as a predictive biomarker of mortality in patients with COVID-19. A high NLR ( $>7.45$ ) is associated with 1.63 times higher risk of death and an increased need for organ support.

Qin et al (10) reported patients with severe COVID-19 had a mean NLR of 5.5 versus 3.2 in nonsevere courses. NLR is

elevated due to a decrease in lymphocytes, particularly CD4+ T-cells, which are responsible for stimulating other immune cells to fight infection and coordinating the immune response. We had similar findings in our cohort, where 84.6% of high NLR patients had low lymphocyte counts ( $ALC < 1.00 \times 10^9/L$ ).

Other studies have correlated low lymphocyte counts with inferior outcomes after COVID-19. In one study, early functional exhaustion of cytotoxic lymphocytes enhanced disease progression (2). Yang et al (6) found elevated NLR and advanced age to predict poor clinical outcome in 93 patients with COVID-19. Finally, a study of 222 patients by Zhang et al (11) found baseline NLR and IgG response; both had predictive capabilities in distinguishing between the severe and nonsevere COVID-19 patients.

## CONCLUSIONS

This study provides evidence that a high baseline NLR is associated with poor prognosis, increased organ support requirements, and mortality. Additional research is warranted to fully understand the significance of the NLR in COVID-19 and mechanisms to modulate this biomarker to improve clinical outcomes.

1 Department of Critical Care Medicine, Respiratory Institute, Cleveland Clinic Foundation, Cleveland, OH.

2 Department of Quantitative Health Sciences, Cleveland Clinic Foundation, Cleveland, OH.

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For information regarding this article, E-mail: [kinga17@ccf.org](mailto:kinga17@ccf.org)

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