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The neutrophil/lymphocyte ratio as a prognostic factor in COVID-19 patients: a case-control study

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Abstract. – OBJECTIVE: SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) has been identified in China as responsible for viral pneumonia, now called COVID-19 (Coronavirus Disease 2019). Patients infected can develop common symptoms like cough and sore throat, and, in severe cases, acute respiratory syndrome and even death. To optimize the available resources, it is necessary to identify in advance the subjects that will develop a more serious illness, therefore requiring intensive care. The neutrophil / lymphocyte ratio (NLR) parameter, resulting from the blood count, could be a significant marker for the diagnosis and management of risk stratification.

PATIENTS AND METHODS: A retrospective, single-center case-control observational study was conducted. The differential cell count of leukocytes, the NLR and the clinical course of patients hospitalized in intensive care with COVID-19 were analyzed, comparing them with other patients (COVID-19 and non-COVID-19) and healthy individuals selected among workers of the Teaching Hospital Policlinico Umberto I in Rome.

RESULTS: 370 patients (145 cases and 225 controls) were included in the case-control study, 211 males (57%) and 159 females (43%). The average age of the population was 63 years (SD 16.35). In the group of cases, out of 145 patients, 57 deaths and 88 survivors were recorded, with a lethality rate of 39.3%. The group of cases has an NLR of 7.83 (SD = 8.07), a much higher value than the control group where an NLR of 2.58 was recorded (SD = 1.93) (p <0.001). The Neutrophils / Lymphocytes ratio may prove to be a diagnostic factor for COVID-19, an NLR> 3.68 revealed an OR 10.84 (95% CI = 6.47 - 18.13) (p <0.005).

CONCLUSIONS: The value of NLR considered together with the age variable allows a risk stratification and allows the development of diagnostic and treatment protocols for patients affected by COVID-19. A high neutrophil to lymphocyte ratio suggests worse survival. Risk stratification and management help alleviate the shortage of medical resources and reduce the mortality of critically ill patients.

Key Words:
Neutrophil to Lymphocyte ratio, Case-control, Prognosis, COVID-19.

Introduction

Since December 2019, cases of SARS-CoV-2-related severe acute respiratory syndrome, now known as COVID-19, have rapidly spread from Hubei Province, China, to the world[1]. The World Health Organization (WHO) has recognized COVID-19 as a pandemic and all countries are facing enormous challenges in trying to prevent further spread as well as treating the growing number of infected patients. Indeed, although most cases are usually self-limiting with mild symptoms such as low-grade fever and cough, the disease can become fatal[2]. Severe cases of COVID-19 can develop severe pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ failure leading to death[3].

SARS-CoV and MERS-CoV infections are characterized by fast and robust initial virus rep-

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lication with late IFN generation, resulting in disproportionate inflammatory host responses provoking grave lung alterations[4,5]. In the fight between the virus and the human body, the immunity of the subjects reduces and the virus virulence augments[6]. This causes edema and congestion of the lung, thickening of the interstitial tissue, and augmented exudation in the alveolar space able to cause respiratory failure.

Similar to patients with Middle Eastern respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), dysregulated inflammation leading to cytokine storms is associated with worsening clinical outcomes in patients with COVID-19[7,8]. This reaction worsens the clinical status of the patient who requires advanced management requiring a bed in intensive care and mechanical ventilation[9]. Emerging evidence suggests that peripheral blood neutrophil to lymphocyte ratio (NLR) can be used as a marker of systemic inflammation[10]. Playing inflammation a crucial role in the pathophysiology of the virus, attention has been paid to the NLR, which provides an indirect index of the patient's inflammatory state and is already widely experienced as a predictor of worsening of various pathologies, solid tumors and other chronic diseases such as respiratory, cardiovascular and renal[11].

Recently, several studies have reported that NLR can differentiate between mild/moderate and severe/critical groups and the likelihood of death in patients with COVID-19 infection. Furthermore, a number of studies[12,13] have suggested that NLR is a reliable predictor of COVID-19 progression and high NLR is associated with high mortality. NLR is calculated as the absolute neutrophil count divided by the absolute lymphocyte count, and 95% of healthy adult subjects have a ratio between 0.78 and 3.53[14]. A single-center retrospective case-control study was conducted in a hospital in Rome to compare NLR values in severe, moderate and mild COVID-19 patients with COVID-19 negative patients. Furthermore, these NLR values were compared with a sample of healthy hospital employees. In the context of a global pandemic, it is therefore of paramount importance to identify which individuals with a disease in an initially mild or moderate state will progress to a severe or critical state, in fact this would allow for early treatment aimed at preventing worse outcomes as well as significant savings of medical and economic resource.

Patients and Methods

Study Design

A single-center, case-control study was conducted. The differential cell count of leukocytes (lymphocytes and neutrophils) and the clinical course of patients hospitalized in (ICU) with COVID-19 were analyzed, comparing them with other patients (COVID-19 and non-COVID-19) and healthy individuals selected from the workers of the Teaching Hospital Policlinico Umberto I in Rome, not affected by COVID-19. The study was conducted from 1/08/2020 to 22/09/2020 and was approved by the Ethics Committee of the Teaching Hospital.

Data Collection

Data were collected retrospectively in the following wards. In the Unit of Anesthesiology and Resuscitation (ICU) the values of leukocytes, lymphocytes and neutrophils of 65 patients hospitalized from 06/03/2020 to 19/05/2020 COVID-19 positive were collected and analyzed. The age range of the patients examined was 20-86 years. The values relating to the first blood counts performed on the patient during hospitalization were reported to assess the performance of the NLR, that was determined on the basis of the first blood sample collected at the hospital entry. Moreover, NLR was determined from a blood sample taken before the diagnosis of COVID-19 or of the status of being a control. In this case the "exposure" is defined before the definition of the status of the patients enrolled. Patients of this group belong to cases. In the Unit of Infectious Diseases, the leukocytes, lymphocytes and neutrophils values of 80 patients hospitalized from 04/02/2020 to 19/05/2020 COVID-19 positive were collected and analyzed. The age range of the patients examined was 20-95 years. The values relating to the first and last blood counts performed on the patient during hospitalization were reported to assess the performance of the NLR. Patients of this group belong to cases. They are patients with mild and moderate disease and an altered NLR. For the choice of controls, the matching technique for gender was used. In the Unit of General Surgery, the values of leukocytes, lymphocytes and neutrophils of 40 patients hospitalized from January 2020 to August 2020 COVID-19 negative were collected and analyzed. The age range of the patients examined was 55-98 years.

In the Unit of Orthopedics and Traumatology, the values of leukocytes, lymphocytes and neutro-

phils of 60 patients admitted from October 2019 to March 2020 COVID-19 negative were collected and analyzed. The age range of the patients examined was 47-88 years.

In the Unit of Otorhinolaryngology, the values of leukocytes, lymphocytes and neutrophils of 31 patients hospitalized from October 2019 to September 2020 COVID-19 negative were collected and analyzed. The age range of the patients examined was 22-77 years.

In all of these surgical wards the values of the first blood count performed on the patient before surgery (in election) were reported to evaluate the value of the NLR. Patients in these groups belong to controls. The values of the last blood count were not entered since the post-operative period and the possible use of corticosteroid therapy could alter these values.

Finally, the values of the leukocyte formula of 94 hospital employees were collected directly in the Unit of Occupational Medicine, extracting data from medical records, chosen with a random method. Only employees with blood chemistry tests performed from 01/10/2019 to 30/06/2020 were included in the study. The age range taken into consideration was 24-68 years. NLR is evaluated in healthy individuals, negative for COVID-19.

Inclusion and Exclusion Criteria

Inclusion Criteria

- COVID-19 positive patients admitted to the Unit of Intensive Care.
- Patients admitted to the Unit of Infectious Disease (COVID-19 Area).
- Patients admitted to Unit of Surgery, Orthopedics, Otolaryngology, negative for COVID-19 (elective surgery).
- Healthy hospital employees who have had routine blood chemistry tests not affected by COVID-19.

Exclusion Criteria

- Employees tested positive for swab and/or serological;
- Employees with acute cancer;
- Patients with recent acute myocardial damage;
- Patients who have recently undergone surgery.

Parameters and Variables

The NLR ratio is evaluated through blood chemistry tests of all patients admitted to ICU and Infectious Diseases and this value is correlated with the age and clinical status of the patients. The values of the NLR are compared with the values of the workers of the Teaching Hospital not affected by COVID-19 and with patients, not COVID-19, admitted to the Surgery, Orthopedics and Otorhinolaryngology Units.

Statistical Analysis

Statistical analysis involved the use of frequency and contingency tables.

Parametric and non-parametric tests were performed to evaluate the differences for the different variables in the 6 groups considered, based on their distribution. IBM SPSS software, version 25.0 (Armonk, NY, USA) was used for the statistical analysis. The significance level was set at $p < 0.05$. All data are presented as means ± SD or median (range). The operating curve of the receiver (ROC) and the area under the curve (AUC) were calculated to compare the differences in the NLR and obtain the cut-off for the case-control analysis and for the analysis between cases only. The following analyses were carried out:

- Univariate analysis, using Chi-square test for qualitative variables; Student's *t*-test and ANOVA for quantitative variables with normal distribution; Mann-Whitney and Kruskal-Wallis tests for quantitative variables with not normal distribution.
- Bivariate analysis using Pearson and Spearman correlation coefficient to evaluate the correlation between quantitative variables.
- Multivariate analysis with multiple linear regression using as dependent variable NLR.
- Multivariate analysis with logistic regression and two outcome models:

  a) to be case, considering cases and controls.
  b) to be dead, considering only cases.

Results

A single-center observational case-control study was conducted to compare the NLR values in the group of virus-positive patients with negative ones and also to analyze the differences in NLR between positive patients but who developed a different disease in terms of severity.

The group of cases is made up of positive COVID-19 patients while the control group is made up of COVID-19 negative patients and employees of the Teaching Hospital.

A total of 370 people, 145 COVID-19 positive and 225 negative patients were enrolled in the study.

The group of COVID-19 positive patients was stratified according to the status of the developed disease. The group of mild/moderate cases consists of 80 patients admitted to the Unit of Infectious Diseases, the group of severe cases consists of 65 patients admitted to the ICU.

The control group consists of 94 healthy hospital employees, 40 patients hospitalized at the UNIT of General Surgery, 60 patients admitted to the Unit of Orthopedics, 31 patients admitted to the Unit of Otolaryngology, all negative for COVID-19 and elective patients.

The sample included in the study consisted of 211 males (57%) and 159 females (43%).

The average age was 63.22 years (SD = 16.351), in the control group the average age is 60.69 years (SD = 15.378), in the group of cases 67.15 (SD = 17.07) (Table I).

In ICU 65 patients were hospitalized and 41 (71.9%) died, while 24 (27.3%) were survivors.

In the Infectious Diseases Unit 80 patients were hospitalized, of which 16 deaths (28.1%) and 64 survivors (72.7%).

The lethality rate recorded was 71.9% in the ICU and 28.1% in the Infectious Diseases Unit (total fatality rate 39.3%).

The group of cases showed a mean value of NLR of 7.83 (SD = 8.07), a much higher value than the group of controls (mean NLR = 2.58; SD = 1.93) (p <0.001).

Univariate Analysis

Comparing patients of ICU and Infectious Diseases Unit, a significant difference (p<0.001) between the NLR of patients with severe disease compared to those suffering from a mild/moderate form (10.06 *vs.* 6.02) was found. This suggests that the NLR is closely related to the severity of the disease (Figure 1).

Patients admitted to the ICU wards show a much higher NLR than patients admitted to COVID-19 negative wards and healthy hospital employees.

Bivariate Analysis

A bivariate analysis was performed for age and gender related to NLR (Table II).

Cases showed NLR values significantly higher (7.83) than controls (2,.8) (p< 0.001).

The results showed that with increasing age, the NLR increases. A younger age of 62 found an NLR of 3.17 (3.08) while an older age of 62 had a NLR of 5.33 (p <0.001).

The NLR values in the young and middle-aged groups did not differ between the two study populations.

On the other hand, there are no significant differences for gender (p> 0.05).

Multivariate Analysis

A multivariate analysis was performed that allows predicting the NLR value as a function of the independent variables (Table III).

Considering all the participants, cases and controls, we get the following results:

Two ROC curves were plotted. Considering all the case-control participants, the area under the curve (AUC) of the first ROC curve (Figure 2A) revealed an area of 0.665 (SD 0.47- p<0.001) with a sensitivity of 0.850 and a specificity of 0.669 (95% CI 0.573-0.757), for a cut-off of 3.70 in relation to being a case.

On the other hand, considering only patients with COVID-19, the area under the curve (AUC)

Table I. Characteristcs of the study population.

Variables	Controls n (%) or Mean (SD)	Cases n (%) or Mean (SD)	*p*-value
Participants	225	145	
Sex			0.353
Female	101 (44.9%)	58 (40%)	
Male	124 (55.1%)	87 (60%)	
Age			<0.05
Age	60.69 (15.37)	67.15 (17.07)	
Ward			<0.05
Intensive care unit		65 (44.8)	
Infectious diseases		80 (55.2)	
Otolaryngology	31 (13.8)		
Surgery	40 (17.8)		
Orthopedics	60 (26.6)		
Occupational Medicine	94 (41.8)		

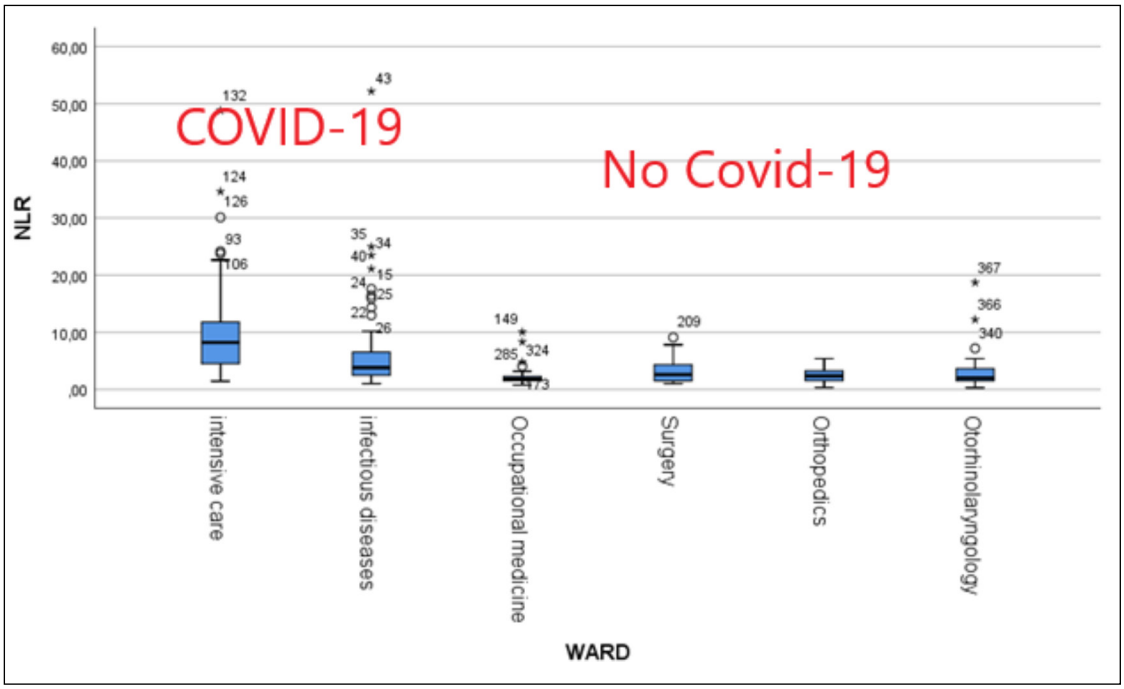

Figure 1. Box plots - Patients admitted to the ICU wards show a much higher NLR than patients admitted to COVID-19 negative wards and compared to healthy hospital employees.

of the second ROC curve (Figure 2B) revealed an area of 0.821 (SD 0.23 $p<0.001$) with a sensitivity of 0.694 and a specificity of 0.543 95% CI 0.776-0.867), for a cut-off of 4.00 in relation to mortality.

Considering only the cases (hospitalized in resuscitation and infectious diseases), we obtain the following results (Table IV).

Multiple Logistic Regression Analysis

Two multiple logistic regression analyzes were conducted, with the outcome variable:

a) Diagnostic factor - being a case (COVID-19) considering all the participants;

b) Prognostic factor - being dead among cases (COVID-19).

If a patient has an NLR> 3.70, the OR of being a case is 10.84 (95% CI 6.47-18.13).

This value makes the NLR a diagnostic factor for COVID-19 (Table V).

On the other hand, the prognostic factor of death (145 patients considered) with an NLR> 4 has an OR of 1.88 but this result is not significant (95% CI = 0.71-5.0) (Table VI).

Table II. Average neutrophil to lymphocyte ratio (NLR) table in relation to gender and age, considering all the patients recruited in the study.

Variables	NLR (average o SD)	*p*-value
Sex		
Male	4.57 (5.35)	0.832
Female	4.34 (5.46)	
Age		
≤ 62 years old	3.17 (3.08)	0.001
> 62 years old	5.33 (6.37)	
Study population		
Cases	7.83 (8.07)	<0.001
Controls	2.58 (1.93)	

Discussion

This study was carried out at the Teaching Hospital Umberto I in Rome on 370 individuals, with the aim of comparing the NLR in patients with COVID-19 (145 cases) and in the negative ones (225 controls). Linear regression analysis performed using NLR as a dependent variable showed that the highest NLR values were found among the cases (highest values in intensive care patients). The NLR value in the control group was similar for all four groups analyzed, with the lowest value in the healthy healthcare workers group.

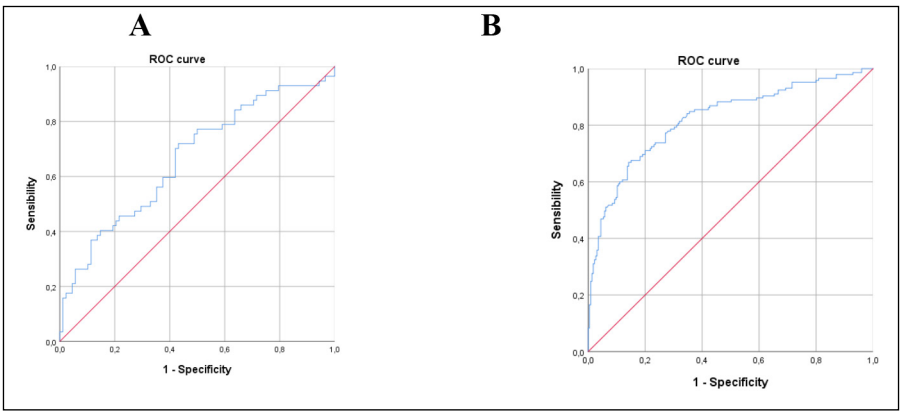

Figure 2. ROC Curves of NLR ratios for **A)** being a case, considering all the patients; and **B)** death, considering only COVID-19 patients.

The ROC-curve analyses demonstrated a diagnostic indication for NLR over 3.70 and a prognostic indication of 4.00 in relation to mortality. However, the significance of this cut-off is different. Using the logistic regression analysis for case-controls individuals, a value of NLR over 3.70 indicates a very high odds of being a COVID-19 case. On the other hand, considering only COVID-19 patients, a value of NLR over 4.00 indicates an almost significant double odds of being dead.

Our results are in agreement with the literature analyzed regarding the association between higher NLR values and worse clinical status[15-17].

Patients with worsening disease have more marked leukocytosis, neutrophilia, lymphopenia and thrombocytopenia than those with moderate disease[18].

Our results are in agreement with those studies in which severe COVID-19 cases had an increase of the neutrophil counts and they had an altered neutrophil count and a lower lymphocyte count, compared to non-serious cases[19-21].

A recent cohort study involving 452 hospitalized patients reinforced the theory that a NLR is significantly higher in patients with severe COVID-19[22]. In this study, a higher NLR upon admission to hospital was associated with a more

Table III. Multivariate analysis considering all the patients. Dependent variable: NLR.

	BETA coefficients Standardized	*p*-value
Age, per one additional year	0.166	0.001
Female gender	0.40	0.375
Ward		
Intensive Unit Care	-	
Infectious diseases	-0.268	<0.001
Surgery	-0.352	<0.001
Orthopedics	-0.488	<0.001
Otolaryngology	-0.300	<0.001
Occupational medicine	-0.514	<0.001

Table IV. Multivariate analysis considering only COVID-19 patients

	Standardized beta coefficients	*p*-value
Age, per one additional year	1.101	0.178
Female gender	0.540	<0.001
Infectious diseases Ward	0.112	<0.001
Otolaryngology	-0.300	<0.001
Occupational medicine	-0.514	<0.001

Table V. Results of multiple logistic regression-dependent variable: being case of COVID-19.

Variables	Full model OR (95% CI)	Stepwise model OR (95% CI)
Female gender	0.85 (0.51-1.40)	
Age, per one additional year	1.013 (1.00-1.029)	1.013 (1.00-1.029)
NLR >3.69	10.84 (6.47-18.13)	10.91 (6.52-18.30)

severe consequence of the patient's future hospitalization. In particular, a NLR> 4 was a predictor of ICU admission.

Some studies[14,23,24] have shown a prognostic value of NLR in various pathological conditions. However, this did not happen in our sample, probably due to the relatively small number of sample. On the other hand, the diagnostic value of the NLR highlighted by the logistic regression (dependent variable "being case") is in agreement with a case-control study conducted by Nalbant et al[25], where an NLR ratio> 2.4 is diagnostic for COVID-19, with the possibility of being positive for the virus which is twenty times greater.

Limitations

Some limitations must be acknowledged. First of all, in relation to mortality, the study needs a larger population. Studies conducted with a larger group of patients would better illustrate the importance of the Neutrophil/Lymphocyte ratio in the prognosis of patients with COVID-19.

Moreover, a control group with similar clinical presentation to cases (i.e., severe respiratory infection) was not included. Ideally, this type of group could be the best comparison to inform about the predictive value of NLR for anticipating the COVID-19 diagnosis. In addition, for all the patients recruited the registration of chronic conditions was not possible, due to the heteogeneity of data collections in the different wards. Finally, cases and controls were different in age, mainly due to the controls in the group of occupational medicine. However, this variable was controlled in the analysis, even if a perfect comparability cannot be achieved.

Conclusions

The NLR is a rapid, widely available, and evaluation relatively inexpensive marker.

This study confirms the association between NLR and the clinical status of the patients, and suggests the possibility to use this ratio as a prognostic index. This study also confirms, according to literature, a higher NLR values in Sars-CoV-2 positive patients than in negative ones.

Future studies should compare the trend of NLR with the progression of the disease and may be necessary to provide more solid knowledge and to deepen in specific aspects of relationship between NLR and prognosis.

Ethical Considerations

This study was conducted in line with research regulations, including the approval of the Ethics Committee of the Teaching Hospital Policlinico Umberto I according to the principles of the "Declaration of Helsinki of the World Medical Association".

Acquisition of Informed Consent and Data Processing

The study involving 370 participants was reviewed and approved by the Ethics Committee of the Teaching Hospital Policlinico Umberto I. Written informed consent for participation was not required for this study in accordance with national legislation and institutional requirements.

Table VI. Results of multiple logistic regression - dependent variable: being dead among COVID-19 cases (145 patients).

Variables	Full model OR (95% CI)	Stepwise model OR (95% CI)
Female gender	0.55 (0.22-1.37)	
Age, per one additional year	1.1 (1.06-1.14)	1.1 (1.06-1.14)
Infectious Diseases Ward	0.13 (0.05-0.34)	0.1 (0.04-0.26)
NLR > 4	1.88 (0.71-5.0)	

Conflicts of Interest

The authors state that the research was conducted in the absence of any business or financial relationship that could be construed as a potential conflict of interest.

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