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ORIGINAL ARTICLE

Neutrophil-to-Lymphocyte Ratio as a Poor Prognostic Factor in Iranian COVID-19 Patients

Ebrahim Kouhsari [1, 2], Nourkhoda Sadeghifard [2], Mohammad Karimian [3], Hojjat Sayyadi [4], Ali Nazari [5], Ali A. Mozafari [6], Hossein Kazemian [2], Hassan Valadbeigi [2], Mohammad R. Kaffashian [7, 8]

[1] *Laboratory Sciences Research Center, Golestan University of Medical Sciences, Gorgan, Iran*
[2] *Clinical Microbiology Research Center, Ilam University of Medical Sciences, Ilam, Iran*
[3] *Department of Surgery, School of Medicine, Emam Khomeini Hospital, Ilam University of Medical Sciences, Ilam, Iran*
[4] *Department of Biostatistics, Faculty of Health, Ilam University of Medical Sciences, Ilam, Iran*
[5] *Department of Infectious Disease, School of Medicine, Shahid Mostafa Khomeini Hospital, Ilam University of Medical Sciences, Ilam, Iran*
[6] *Clinical Research Development Unit, Shahid Mostafa Khomeini Hospital, Ilam University of Medical Sciences, Ilam, Iran*
[7] *Department of Physiology, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran*
[8] *Student Research Committee, Ilam University of Medical Sciences, Ilam. Iran*

SUMMARY

Background: **We aimed to accumulate evidence that suggests the potential role of neutrophil-to-lymphocyte ratio (NLR) in determining the prognostic factor for COVID-19 patients.**
Methods: **A cohort of COVID-19 hospitalized patients at the Ilam University of Medical Sciences was analyzed. Logistic regression models were performed to identify the potential role of NLR in determining the prognostic factor for COVID-19 patients.**
Results: **The total number of in-hospital mortality was 43/328 (13.1%). Multivariate analysis identified that there was a 26% higher risk of in-hospital death for each unit increase in NLR (Odds ratio [OR] = 1.08; 95% confidence interval [95% CI], 1.01 to 1.14; p = 0.0147). Multivariate analysis identified that there was an 8% higher risk of in-hospital death for each unit increase in NLR (Odds ratio [OR] = 1.08; 95% confidence interval [95% CI], 1.01 to 1.14; p = 0.0147). Compared with patients in the NLR < 5 group, the NLR of patients in the NLR ≥ 5 group had a 16-fold higher risk of mortality (OR = 16.04; 95% CI, 1.14 to 224.95; p = 0.0395) after adjustment for potential confounders.**
Conclusions: **NLR is an independent risk factor of mortality COVID-19 patients.**
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Correspondence:
Mohammad Reza Kaffashian, Associate Professor
Banganjab, Pazhouhesh Blvd
Ilam University of Medical Sciences
P.O. Box: 6939177143
Ilam
Iran
Phone: +98 9183412354
Fax: +98 8432227120
Email: m_r_kaffashian@yahoo.com

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KEY WORDS

COVID-19, neutrophil-to-lymphocyte ratio, poor prognosis

LIST OF ABBREVIATIONS

NLR - Neutrophil-to-Lymphocyte Ratio
OR - Odds ratio
2019-nCoV - 2019 novel coronavirus
WHO - World Health Organization
WBC - White blood cell count
CIs - Confidence intervals

BUN - Blood urea nitrogen
ALT - Alanine aminotransferase
AST - Aspartate aminotransferase
LDH - Lactate dehydrogenase
ALP - Alkaline phosphatase
APTT - Activated partial thromboplastin time
MERS-CoV - Middle East respiratory syndrome coronavirus
VEGF - Vascular endothelial growth factor
ARDS - Acute Respiratory Distress Syndrome

INTRODUCTION

Since December 2019, an outbreak cluster of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) developed in Hubei Province in China, now known as COVID-19 (coronavirus disease 2019) that causes the major public health threats worldwide [1,2]. The World Health Organization (WHO) announced that the epidemic of COVID-19 had become a global pandemic [3]. Up to now, there is no successful and specific therapy for COVID-19, and the treatment approaches are mainly supportive; therefore, it is essential to characterize risk factors as a prognostic factor for COVID-19 patients. Several abnormal hematological parameters associated with COVID-19 patients included lymphopenia, *neutrophilia*, thrombocytopenia, and abnormally increased liver enzyme levels [4-7]. The neutrophil to lymphocyte ratio (NLR) as a systemic inflammatory marker of immune-mediated, metabolic, prothrombotic, and neoplastic diseases, can be simply assessed during routine hematology, and numerous reports indicated that NLR had potential as a predictor for prognosis in various diseases [4-7]. Also, recently published literature has revealed that an increase in the NLR was related with the severity or death due to COVID-19 [8-12]. Whether NLR could be an independent factor of death in COVID-19 patients requires further clarification. We aimed to assess the prognostic value of NLR for mortality in Iranian patients with COVID-19.

MATERIALS AND METHODS

Study design, and patients

This research was a retrospective single-center study, which recruited 349 hospitalized patients with COVID-19 in Shahid Mostafa Khomeini Hospital (Ilam, Iran) from March 20, 2020, to May 8, 2020. The diagnosis of COVID-19 was based on the World Health Organization interim guidance [13]. Only the laboratory-confirmed cases were included in the research. The exclusion criteria were patients were pregnant, had hematological diseases, or had missing baseline data.

Baseline data collection

The baseline data, including epidemiological history and laboratory characteristics, were rerecorded and reviewed. All data were gathered with a customized program from the hospital electronic health record. The samples for peripheral venous blood were gathered on admission or during the hospital stay and were assessed at the central, clinical laboratory of Shahid Mostafa Khomeini hospital following standard operating procedures. The routine blood tests (including red blood cell count, white blood cell count [WBC], leukocyte subtypes, hematocrit count, hemoglobin count, and platelet count) were made using the Sysmex KX-21 automated hematology analyzer (Sysmex Corporation, Kobe, Japan). All patient information is kept confidential. Patients were diagnosed clinically (lung radiographical features) and also confirmed using laboratory-based data (RT-PCR by throat and nose swab specimens from the upper respiratory tract).

Statistical analysis

Demographic and clinical characteristics of all cases were expressed as frequencies and proportions for categorical variables, and we used mean ± SD for continuous variables. The relationships between categorical variables were assessed using the chi-squared test and *t*-tests were used for comparing the group means of the outcome of in-hospital death. We used univariate and multivariate logistic regression to assess the effectiveness of laboratory parameters. Unadjusted and adjusted odds ratio (ORs) and 95% confidence intervals (CIs) were calculated in these models. In the multivariate-adjusted models, age, smoking status, white blood cells, hematocrit, C-reactive protein, and hemoglobin were included. $p < 0.05$ was recognized as statistically significant. All these statistical calculations were performed using the SPSS 17.0 software (SPSS Inc, Chicago, IL, USA) and R 3.5.2 (http://www.R-project.org).

RESULTS

Of the 328 laboratory-confirmed patients with COVID-19 included in our study, the median age of patients was 59 years (IQR 43 - 70), ranged from 3 years to 96 years, and 53% (n = 185) were male. The total number of in-hospital mortality was 43 (13.1%). Comparison of the baseline epidemiologic and laboratory features of COVID-19 patients by median NLR value (NLR < 5 and NLR ≥ 5) is depicted in Table 1. Compared with patients in the NLR < 5 group, patients in the NLR ≥ 5 group were older, more likely to be male. The incidence of mortality was considerably elevated when comparing the NLR groups (9.2% vs. 23.6% for NLR < 5 vs. NLR ≥ 5, respectively). A significant difference showed between baseline variables including gender, WBCs, blood urea nitrogen (BUN), and erythrocyte sedimentation rate in a comparsion between the two NLR groups (NLR < 5 and NLR ≥ 5) ($p < 0.05$). Table 2 depicts the univariate logistic regression models between variables and mortality. The univariate analysis indicated that age (OR = 1.033, 95% CI, 1.014 - 1.053, p = 0.001), WBC

Table 1. Baseline characteristics of COVID-19 patients according to the neutrophil-lymphocyte ratio (NLR) group (n = 328).

Variable	NLR (< 5, n; 239)	NLR (≥ 5, n; 89)	p-value
	Mean ± standard deviation (SD)	Mean ± standard deviation (SD)	
Demographic			
Age, years	56.34 ± 17.47	58.61 ± 20.73	0.36
Male (%)	117 (67.2)	57 (32.8)	0.015
Female (%)	122 (79.2)	32 (20.8)	
BMI (kg/m^2)	25.78 ± 3.43	25.89 ± 2.77	0.77
Smoking (%)	11 (6.5)	7 (10.3)	0.326
ICU stay (days)	7.29 ± 6.91	4.42 ± 6.20	0.099
Laboratory			
White blood cells, 10^9/L	7.13 ± 76.65	10.7 ± 7.1	< 0.001
Lymphocyte (%)	28.16 ± 11.83	11.83 ± 3.4	< 0.001
Neutrophil (%)	70.21 ± 11.86	87.07 ± 3.85	< 0.001
Red blood cells, 10^12/L	4.53 ± 1.69	4.29 ± 0.70	0.20
Hemoglobin, gm/dL	12.85 ± 1.99	12.73 ± 2.21	0.63
Platelet, 10^9/L	222.36 ± 181.68	234.46 ± 104.00	0.56
ALT, U/L	50.38 ± 72.74	59.90 ± 97.76	0.44
AST, U/L	49.51 ± 63.17	71.88 ± 141.30	0.25
LDH, U/L	667.14 ± 782.71	700.79 ± 347.78	0.73
CK, U/L	238.11 ± 802.57	328.50 ± 496.24	0.46
ALP, U/L	228.937 ± 114.234	309.057 ± 236.355	0.13
Glucose, mg/dL	142.27 ± 150.37	147.12 ± 130.58	0.81
Blood urea nitrogen, mg/dL	36.50 ± 25.96	57.89 ± 49.12	< 0.001
Creatinine, mg/dL	1.43 ± 1.63	1.64 ± 1.82	0.31
D-dimer, mg/L	0.37 ± 0.42	0.39 ± 0.40	0.91
PT, sec	14.27 ± 17.65	12.72 ± 2.52	0.49
APTT, sec	16.17 ± 16.21	14.39 ± 18.23	0.47
Total bilirubin, mg/dL	4.97 ± 19.12	8.77 ± 17.35	0.35
Erythrocyte sedimentation rate, mm/hr	43.19 ± 33.36	55.52 ± 31.69	0.004
Total protein	6.33 ± 0.56	6.45 ± 0.21	0.78
Hematocrit (%)	37.88 ± 6.94	37.17 ± 7.74	0.42
Calcium, mg/dL	9.55 ± 1.06	9.34 ± 0.50	0.39
Sodium, mEq/L	136.77 ± 9.43	136.92 ± 6.82	0.89
Potassium, mEq/L	4.16 ± 3.29	4.26 ± 3.28	0.79
Albumin, g/dL	10.48 ± 34.86	106.460 ± 34.81	0.37
Death (%)	22 (9.2)	21 (23.6)	0.001

(OR = 1.00, 95% CI, 1.00 - 1.00, p = 0.004), alanine aminotransferase (ALT) (OR = 1.004, 95% CI, 0.001 - 1.008, p = 0.023), aspartate aminotransferase (AST) (OR = 1.006, 95% CI, 1.002 - 1.010, p = 0.004), lactate dehydrogenase (LDH) (OR = 1.001, 95% CI, 1.00 - 1.001, p = 0.019), alkaline phosphatase (ALP) (OR = 1.004, 95% CI, 1.001 - 1.008, p = 0.007), BUN (OR = 1.023, 95% CI, 1.00 - 1.045, p = 0.049), total bilirubin (OR = 1.01, 95% CI, 1.00 - 1.02, p = 0.0094), activated partial thromboplastin time (APTT) (OR = 1.023, 95% CI, 1.00 - 1.046, p = 0.049) were positively correlated with the risk of in-hospital death. Table 3 displayed the results of the univariate and multivariate logistic regression models assessing the association between NLR and death. In the unadjusted model, there was a 12% increase in risk of mortality per unit increase in NLR (OR

Table 2. The unadjusted association between baseline variables and death (n = 328).

Variable	Statistics	Odds ratio (95% CIs)	p-value
Age, years	57.7 ± 4.07	1.033 (1.014, 1.053)	0.001
Gender Male	185 (53%)	1.0	0.113
BMI (kg/m^2)	23.8 + 0.57	0.966 (0.879, 1.062)	0.479
Smoking No	239 (68.5%)	1.0	0.737
ICU stay (days)	3 + 1.2	0.962 (0.889, 1.040)	0.33
White blood cells, 10^9/L	10.9 + 2.75	1.00 (1.00, 1.00)	0.004
Lymphocyte (%)	39.2 + 8.2	0.0982 (0.954, 1.010)	0.210
Neutrophil (%)	NA	1.017 (0.988, 1.046)	0.263
Red blood cells, 10^12/L	6.84 + 2.42	0.826 (0.570, 1.197)	0.312
Hemoglobin, gm/dL	43,077 + 25,205	1.00 (1.00, 1.00)	0.690
Platelet, 10^9/L	135,600 + 21,674	1.00 (1.00, 1.00)	0.803
ALT, U/L	31 + 1	1.004 (0.001, 1.008)	0.023
AST, U/L	36.9 + 3.6	1.006 (1.002, 1.010)	0.004
LDH, U/L	532 + 1	1.001 (1.00, 1.001)	0.019
CK, U/L	136.5 + 71.5	1.000 (1.000, 1.001)	0.106
ALP, U/L	NA	1.004 (1.001, 1.008)	0.007
Glucose, mg/dL	105 + 9.3	1.002 (0.996, 1.003)	0.095
Blood urea nitrogen, mg/dL	29.9 + 10.1	1.014 (1.006, 1.022)	< 0.001
Creatinine, mg/dL	1.94 + 0.42	1.141 (0.991, 1.314)	0.067
Total bilirubin, mg/dL	15.77 + 9.2	1.023 (1.00, 1.045)	0.049
Total protein, mg/dL	7.2	0.096 (0.000, 2.712)	0.096
Erythrocyte sedimentation rate, mm/hr	58.3 + 16.8	1.006 (1.00, 1.003)	0.290
Hematocrit (%)	34.5 + 2.56	0.981 (0.942, 1.021)	0.352
Calcium, mg/dL	7.24 + 1.6	1.043 (0.980, 1.110)	0.187
Sodium, mEq/L	115.3 + 22.3	0.991 (0.970, 1.012)	0.409
Potassium, mEq/L	14.5 + 10.6	1.009 (0.980, 1.038)	0.547
Albumin, g/dL	4.15 + 0.25	0.999 (0.992, 1.007)	0.818
D-dimer, mg/L	NA	2.185 (0.348, 13.724)	0.404
APTT, sec	19.7 + 9.4	1.023 (1.00, 1.046)	0.049
PT, sec	12.93 + 0.07	1.002 (0.980, 1.025)	0.848

Table 3. Risk association between baseline NLR and in-hospital death.

	Unadjusted Odds ratio (95% CIs)	p-value	Model 1 ≠ Odds ratio (95% CIs)	p-value
NLR	1.117 (1.040 - 1.199)	0.002	1.261 (1.127 - 1.411)	< 0.001
NLR < 5	0.887 (0.597 - 1.316)	0.550	1.024 (0.588 - 1.784)	0.933
NLR ≥ 5	1.075 (0.986 - 1.172)	0.103	1.307 (1.075 - 1.588)	0.007

≠ Model 1 was adjusted for age, white blood cell, blood urea nitrogen, total bilirubin, alanine aminotransaminase, aspartate transaminase, lactate dehydrogenase.

= 1.117; 95% CI, 1.040 - 1.199; p = 0.002). The OR for NLR ≥ 5 group was not significantly higher than the OR for NLR < 5 group (OR = 1.075; 95% CI, 0.986 - 1.172; p = 0.103). Adjustment for age, BUN, total bilirubin, ALT, AST, and LDH did not reduce the relationship between the NLR and mortality. NLR as a continuous variable was related with 26% increased risk of mortality in the adjusted model (OR = 1.261; 95% CI, 1.127 - 1.411; p < 0.001). Meanwhile, elevated of NLR showed an increase in the risk of mortality for the NLR ≥ 5 (vs. the NLR < 5) with OR of 1.307 (95% CI, 1.075 to 1.588; p = 0.007).

DISCUSSION

In our study, the data of 328 COVID-19 patients were evaluated, the epidemiologic and baseline laboratory characteristics of COVID-19 patients in the NLR groups (< 5 and ≥ 5) were described and compared. The independent risk factors concerning the incidence of death were screened. The percentage of in-hospital death was 14.8%. COVID-19 was caused by a novel coronavirus, which was called 2019 novel coronavirus (2019-nCoV). Hematological abnormalities in leukocytes is one of the significant parameters relating with the severity of the Middle East respiratory syndrome coronavirus (MERS-CoV) disease [14,15]. Recently published literature supporting the association of cytokine storm includes increased levels of inflammatory cytokines, chemokines, and NLR in disease severity [11,15]. These results are in agreement with our outcomes. Older age is considered an independent predictor of mortality [16]. In this study, we adjusted age and other variables to reduce the possible effect of confounding. This link showed in the multivariable regression analyses. The risk of death tended to be higher as NLR elevated in males after adjustment for cofounders were found in other studies [9,17] which was in contrast to our study. More studies should be addressed on other peoples and ethnicities to warrant and approve this outcome and conclude the divergences in the pathophysiological mechanisms between male and female with COVID-19. Several recent reports assessed feasibility of either NLR in predicting prognosis in COVID-19 patients [5,7-10,12]. In particular, Liu et al. [9] proposed an independent risk factor of NLR for death by evaluating the data of a cohort of 245 COVID-19 patients. Additionally, a recent study by Cai et al. [12] suggested that higher NLR could be considered as a predictor for assessing the severity of COVID-19 in a cohort of 432 hospitalized patients. In the present study, NLR as an independent factor was related with 8% increased risk of mortality in COVID-19 patients, which is consistent with recent studies [5,8,9,12]. It supports the theory of a close relationship between hyperinflammatory state and COVID-19 pathogenesis. Neutrophils are definitely an essential component of acute inflammation [18]. Neutrophils discharge huge volumes of oxygen-containing radicals that can cause cell DNA damage and free the virus from the cells. So, antibody-dependent cell-mediated cytotoxicity may directly eradicate the virus, expose virus antigen, and induce cell-specific and humoral immunities [19]. In addition, neutrophils generate several immune effector molecules, such as circulating vascular endothelial growth factor (VEGF). Compared with normal tissues, VEGF has considerably higher expression in COVID-19 patients [21], and the decreased expression of VEGF and VEGFR confers to significantly hindered tissue and organ damage. Additionally, neutrophils can be elicited by virus-related inflammatory factors generated by lymphocyte and endothelial cells [21-23]. Finally, virus-triggered inflammation led to increased NLR, and subsequently higher severity and death. The outcomes directed that 2019-nCoV may act on T lymphocytes mainly CD4+T and CD8+T cells and NLR is a significant factor that causes patients to weaken [24]. Numerous reports have directed the difference of baseline leukocyte counts between the clinical stages in COVID-19 patients.

A study [11] described that the severity of COVID-19 is related to neutrophilia but not lymphopenia in severe cases compared with non-severe cases, therefore the NLR tended to be higher in severity of COVID-19 patients. Mo et al. [17] observed that cases with refractory COVID-19 had higher levels of neutrophils in comparison with other cases. Besides, several studies assessed the clinical features of the 2019-nCoV reactivation. Ye G et al. [25] found that out of the 5 reactivated cases, one case had a higher level of lymphopenia and neutrophilia demonstrating the significant value of leukocyte counts on 2019-nCoV reactivation.

The findings of our study have some clinical suggestions. NLR could be rapidly calculated based on a blood routine test on admission, thus we should pay more attention to these laboratory characteristics to recognize severity in COVID-19 patients at an early stage. The cost-effective and effective marker NLR may help in complicated predictions. Acute respiratory distress syndrome, which is a type of respiratory failure considered by a quick onset of generalized inflammation in the lungs, is the primary cause of death of COVID-19 patients. Thus, higher NLR levels considering an increased inflammatory process may predict a poor prognosis. In this observational study, to reduce potential various confounders, we adopted methods of statistical adjustment. There were also several limitations of this study; (1) this analysis is a single-center, (2) the number of declared results is to some extent small which limits the statistical power of our study, (3) outcomes of our study might not noticeably be used for other ethnicities, since all patients were hospitalized Iranian COVID-19 patients, (4) while we have adjusted for potential confounders, unmeasured confounding factors might not be fully measured, (5) the experimental data are limited.

CONCLUSION

This study performed in the Iranian COVID-19 patients revealed that the NLR is an independent risk factor of mortality COVID-19 patients. We believe that risk predicting can support decrease the lack of medical resources and manage COVID-19. Additionally, this conclusion may differ from the other conclusions and should be developed in more clinical cases. Further studies are necessary to warrant our results and to compare the predictive ability of NLR.

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Ethical Statement:
This study was approved by the Ethics Committee of the Ilam University of Medical Sciences (IR.MEDILAM.REC.1399.021). All study procedures were conducted in accordance with the Helsinki Declaration and its later amendments, or comparable ethical standards.

Declaration of Interest:
None declared.

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