Neutrophil-to-Lymphocyte Ratio Cut-Off Point for COVID-19 Mortality: A Retrospective Study

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Abstract- Several months have passed since the onset of the COVID-19 pandemic. Multiple characteristics have been proposed as prognostic factors so far. This study aims to provide evidence on the association of neutrophil-to-lymphocyte ratio (NLR) at the hospitalization time and three desired outcomes (mortality, prolonged hospitalization, and intensive care unit [ICU] admission). We designed a single-centre retrospective observational study in Baharloo Hospital (Tehran, Iran) from 20 February to 19 April 2020. Patients with confirmed COVID-19 diagnosis via rt-PCR or chest CT imaging were included. Demographic and clinical data were obtained. The sample was divided into three groups, using tertile boundaries of initial NLR. The differences in mortality, comorbidities, hospitalization duration, drug administration, and ICU admission between these three groups were investigated. The identified confounding factors were adjusted to calculate the odds ratio of death, ICU admission, and prolonged hospitalization. Nine hundred sixty-three patients were included. In total, 151 and 212 participants experienced mortality and ICU admission, respectively. In multivariate logistic regression models, the adjusted odds ratio for mortality event in the second and third tertile of initial NLR after full adjustment were 1.89 (95% CI:1.07-3.32) and 2.57 (95% CI:1.48-4.43) and for ICU admission were 1.85 (95% CI:1.14-3.01) and 2.88 (95% CI:1.79-4.61), respectively. The optimal cut-off value of the initial NLR for predicting mortality was 4.27. Initial NLR can predict mortality and ICU admission in COVID-19 patients. Further investigations for curating the calculated cut-off can propose initial NLR as an indicator of poor prognosis for COVID-19 patients.

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Keywords: Blood cell count; Neutrophil-to-lymphocyte ratio; Coronavirus disease 2019 (COVID-19); Mortality; Intensive care units

Introduction

Since December 2019, the COVID-19 infection has impacted more than 119 million people, and more than 2.6 million are deceased (1). On 31 January 2020, the World Health Organization announced COVID-19 as a pandemic (2). This infection caused an immense burden and crisis throughout the world (3).

This virus has broad-spectrum manifestations, from beginning with flu-like symptoms to severe and mortal pneumonia cases, and even may cause acute respiratory distress syndrome (ARDS) (4,5). Even a single study revealed a 42.5% of the infected population were asymptomatic (6).

Several studies were conducted to find the factor related to patients' mortality regarding the high infectivity and fatality of this infection. They found the patient's comorbidities, age, gender, and other mediators

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linked with COVID-19 mortality (7,8).

Scientists cast doubt about the pathogenesis of COVID-19 that causes death. Some believed that cytokine storms and inflammation could lead to organ failure (9,10). Another hypothesized that coagulopathy and bacterial superinfection might be responsible for patients' death (11).

Many articles have revealed that the laboratory findings, such as ESR, CRP, lymphocyte count, neutrophil count, neutrophil-to-lymphocyte ratio (NLR) at the time of admission, have a strong association with the severity and mortality of COVID-19 (12-14). Tanboga *et al.*, used multiple variables such as NLR, LDH, age, gender, Creatinine, D-dimer and proposed a valid model for estimation of COVID-19 patients' prognosis (15).

In another perspective, reverse transcription-polymerase chain reaction (rt-PCR), which is the first way of diagnosing COVID-19, Song *et al.*, showed that it has false negatives in many cases (3).

Based on Han *et al.*,'s findings, NLR is more sensitive among laboratory data in contrast to lymphocyte and neutrophil count as diagnostic factors (16,17). Formerly, an elevation in NLR has shown to be associated with malignancies (18), diabetes (19), metabolic syndrome (20), ankylosing spondylitis (21), acute diverticulitis (22), and cardiovascular diseases (23).

This study aimed to investigate the association between initial NLR and other factors such as death, ICU admission, comorbidities, and drug administration in COVID-19 patients.

Materials and Methods

We designed a single-centre, retrospective observational study in Baharloo Hospital (Tehran, Iran), which is declared as a "specific hospital for COVID-19 patients" by Iran's Ministry of Health and Medical Education (MOHME). The study was aimed to investigate the prognostic value of NLR. This study was approved by the ethics committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1399.197).

Participants

A total of 1300 patients were admitted from 20 February to 19 April 2020. All patients have been admitted due to COVID-19 diagnosis via chest CT imaging or rt-PCR. Only patients who had a record of NLR at least once during their admission time were included (Figure 1). All diagnoses and treatment procedures have complied with the "diagnosis and treatment flowchart" issued by the health deputy of MOHME (24). Due to ethical commitments, the identity of patients was kept confidential.

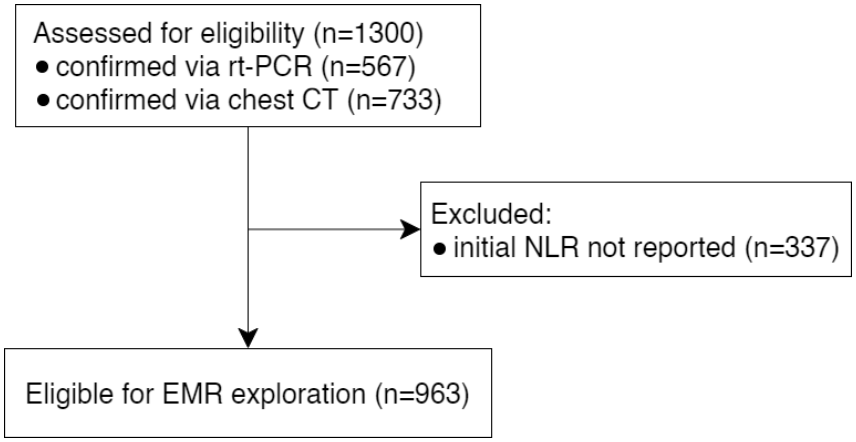

Figure 1. Flow diagram of the study. Amongst 1300 inpatient cases, only 963 patients were eligible to be included in this study (rt-PCR reverse transcription polymerase chain reaction; CT computed tomography; NLR neutrophil-to-lymphocyte ratio; EMR electronic medical record)

Data collection

Demographic characteristics, including gender and age, clinical data, including comorbidities, body mass index (BMI), administered drugs, duration of hospitalization, and ICU admission, were obtained. We extracted these data from electronic medical records (EMR).

For simplification, comorbidities were categorized in 'heart diseases,' including ischemic heart diseases, congestive heart failure and valvular heart diseases,

'respiratory diseases' including tuberculosis, chronic obstructive pulmonary disease, asthma, and 'thyroid disorders' including hyperthyroidism and hypothyroidism. All these conditions were recognized by the patient's history and past diagnosed disorders/illnesses by other clinicians.

Statistical analyses

All data were processed using IBM SPSS Statistics 26. Quantitative variables were reported in the median and standard deviation. Differences between qualitative variables were calculated using the Chi-squared test. According to the Kolmogorov-Smirnov test, none of the quantitative variables were normally distributed; therefore, relations between quantitative and qualitative variables were analyzed using the Mann-Whitney test. $P<0.05$ was considered significant.

For logistic regression, initial NLR was defined as tertile boundaries (initial NLR <2.83; 2.83≤ initial NLR ≤5.26; initial NLR >5.26). Kaplan-Meier survival curves were used to compare the 30-day survival rate for patients within these three ranges. Crude and multiple logistic regression models were used to estimate the Odds Ratio (OR) with 95% confidence intervals (95% CI) of different risk factors for the development of desired outcomes (mortality, ICU Admission, prolonged hospitalization). Prolonged hospitalization was defined as hospitalization days higher than median days of hospitalization for all patients. Quantile boundaries for the distribution of initial NLR generated and its prevalence in each quantile were determined in order to investigate the trends of prevalence of mortality and ICU admission. Lastly, using the receiver operating curve (ROC) analysis and the Youden index, NLR's optimal cut-off value has been calculated.

Results

As shown in Figure 1, a total of 963 patients were included in this study. Of those, 56.2% were male, and a mean age of 56.7 (±17.2) was reported. After dividing the sample into three segments of those with initial NLR <2.83, those with 2.83≤ initial NLR ≤5.26, and those with initial NLR >5.26, a number 320, 324, and 319 people entered each group, respectively. More detailed demographic characteristics and clinical data are available in Table 1.

Table 1. Baseline characteristics and laboratory test of 963 patients

	All patients (n=963)	Group 1 ‡ (n=320)	Group 2 ‡ (n=324)	Group 3 ‡ (n=319)	*P*
Death	151 (15.7)	23 (7.2)	47 (14.5)	81 (25.4)	<0.0001
Age *	56.73±17.21	53.86±16.45	55.43±15.95	60.95±18.39	<0.0001
BMI *	27.82±6.25	29.19±8.82	27.46±26.90	26.90±4.64	0.001
Male	541 (56.2)	147 (45.9)	177 (54.6)	217 (68)	<0.0001
Age ≥ 60 years	420 (43.6)	121 (37.8)	130 (40.1)	169 (53)	<0.0001
Hypertension	314 (32.6)	89 (27.8)	106 (32.7)	119 (37.3)	0.038
Diabetes	282 (29.3)	71 (22.2)	98 (30.2)	113 (35.4)	0.001
Stroke	61 (6.3)	18 (5.6)	13 (4)	30 (9.4)	0.016
Dyslipidaemia	56 (5.8)	20 (6.3)	13 (4)	23 (7.2)	0.205
Heart diseases	144 (15)	35 (10.9)	50 (14.4)	59 (18.5)	0.026
Thyroid disorders	39 (4)	10 (3.1)	19 (5.9)	10 (3.1)	0.126
Respiratory diseases	50 (5.2)	16 (5)	15 (4.6)	19 (6)	0.737
RA/SLE	12 (1.2)	5 (1.3)	3 (0.9)	5 (1.6)	0.762
CKD	27 (2.8)	5 (1.6)	7 (2.2)	15 (4.7)	0.038
Hydroxychloroquine	775 (80.5)	267 (83.4)	265 (81.8)	243 (76.2)	0.052
Lopinavir/Ritonavir	398 (41.3)	122 (38.1)	132 (40.7)	144 (45.1)	0.191
Ribavirin	158 (16.4)	36 (11.3)	52 (16)	70 (21.9)	0.001
Favipiravir	60 (6.2)	20 (6.3)	29 (9)	11 (3.4)	0.016
Corticosteroids	170 (17.7)	30 (9.4)	53 (16.4)	87 (27.3)	<0.0001
ACE inhibitors/ARB	101 (10.5)	28 (8.8)	40 (12.3)	33 (10.3)	0.328
ICU admission	212 (22)	34 (10.4)	65 (20.1)	113 (35.4)	<0.0001
Length of hospitalization (days) †	6 (4)	5 (5)	6 (4)	6 (5)	<0.0001

NOTE: Data are reported as frequency and percent
* Data are mean ± standard deviation
† Data are median and interquartile range (IQ)
‡ Group 1: initial NLR < 2.83; Group 2: 2.83 ≤ initial NLR ≤ 5.26; Group 3: initial NLR > 5.26
NLR neutrophil-lymphocyte ratio; BMI body mass index; RA rheumatoid arthritis; SLE systemic lupus erythematosus; CKD chronic kidney disease; ACE angiotensin-converting enzyme; ARB angiotensin receptor blockers; ICU intensive care unit

Among comorbidities, heart diseases (*P*=0.026), hypertension (*P*=0.038), chronic kidney disease (*P*=0.038), diabetes mellitus (*P*=0.001), and stroke occurrence (*P*=0.016) were significantly associated with initial NLR. In the deceased patients, initial NLR was significantly higher than survived patients (*P*<0.0001). Besides, administrating ribavirin (*P*=0.001), favipiravir (*P*=0.016), and corticosteroids (*P*<0.0001) were associated with initial NLR. The neutrophil-to-lymphocyte ratio was significantly higher in males than in females (*P*<0.0001).

As having significantly different distribution among groups, the factors mentioned above were used to adjust the odds ratio. Regarding the crude odds ratio (Table 2), after adjustment of age, sex, and other confounder factors (hypertension, diabetes, heart diseases, chronic kidney disease, stroke, ribavirin, favipiravir, corticosteroids, hydroxychloroquine), the odds ratio for mortality event in the second and third tertile of initial NLR were 1.89 (95% CI:1.07-3.32; *P*=0.026) and 2.57 (95% CI:1.48-4.43; *P*=0.001) and for ICU admission were 1.85 (95% CI:1.14-3.01; *P*=0.013) and 2.88 (95% CI:1.79-4.61; *P*<0.0001), respectively. Although the relation between initial NLR and prolonged hospitalization (higher than the median) does not seem meaningful in group 3 (OR=1.26; CI 95%=0.88-1.80; *P*=0.199), in group 2, it was rather significant (OR=1.42; CI 95%=1.10-1.99; *P*=0.0.042).

According to the Kaplan-Meier model (Figure 2), the 30-day survival rate was decreased as the initial NLR increased. Also, as shown in the trends of prevalence of mortality and ICU admission (Figure 3), as NLR at the time of admission increased, the mortality (*P*<0.0001) and ICU admission (*P*<0.0001) increased too.

The ROC analysis (Figure 4) revealed that the optimal cut-off value of initial NLR for predicting mortality was 4.27 (sensitivity=70.20%; specificity=60.22%; correctly classified=62.72%).

Table 2. Association between initial NLR and three outcomes (death, ICU admission, prolonged hospitalization)

		Model 1 †	*P*	Model 2 †	*P*	Model 3 †	*P*
Outcome: Death	**Group 1** *	1		1		1	
	Group 2 *	2.19 (1.29-3.70)	0.003	2.13 (1.24-3.66)	0.006	1.89 (1.07-3.32)	0.026
	Group 3 *	4.39 (2.68-7.19)	<0.0001	3.31 (1.97-5.55)	<0.0001	2.57 (1.48-4.43)	0.001
Outcome: ICU Admission	**Group 1** *	1		1		1	
	Group 2 *	2.11 (1.34-3.30)	0.001	2.04 (1.30-3.22)	0.002	1.85 (1.14-3.01)	0.013
	Group 3 *	4.61 (3.02-7.04)	<0.0001	3.86 (2.49-5.97)	<0.0001	2.88 (1.79-4.61)	<0.0001
Outcome: prolonged hospitalization (higher than the median)	**Group 1** *	1		1		1	
	Group 2 *	1.53 (1.11-2.13)	0.010	1.54 (1.11-2.14)	0.009	1.42 (1.10-1.99)	0.042
	Group 3 *	1.59 (1.14-2.21)	0.005	1.57 (1.11-2.21)	0.008	1.26 (0.88-1.80)	0.199

NOTE: Data are odds ratio (confidence interval 95%)

* Group 1: initial NLR < 2.83; Group 2: 2.83 ≤ initial NLR ≤ 5.26; Group 3: initial NLR > 5.26

† Model 1: without adjustment; Model 2: age and sex adjustment; Model 3: model 2 plus other confounders adjusted (hypertension, diabetes, heart diseases, chronic kidney disease, stroke, ribavirin, favipiravir, corticosteroids, hydroxychloroquine)

NLR neutrophil-lymphocyte ratio; ICU intensive care unit

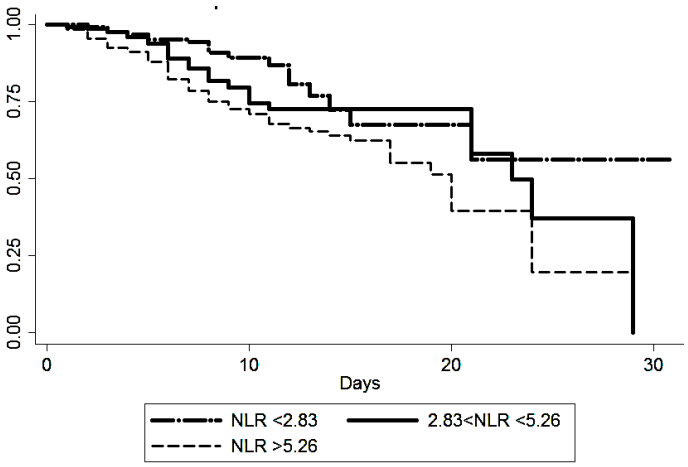

Figure 2. Kaplan–Meier curves of three ranges of NLR for COVID-19. The higher rate of NLR roughly led to a lower survival chance during hospitalization

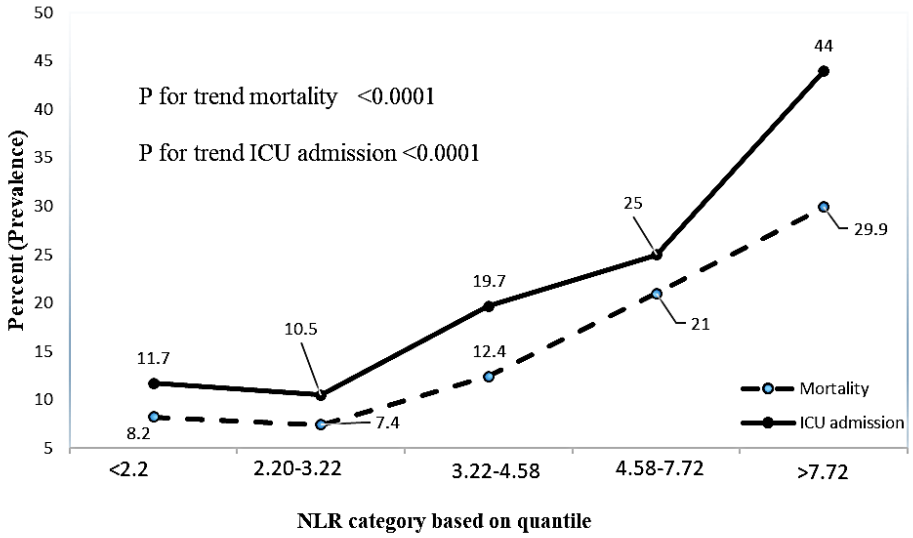

Figure 3. The trend of percent of mortality and ICU admission by increasing NLR. As the NLR raised, the mortality and ICU admission were increased too

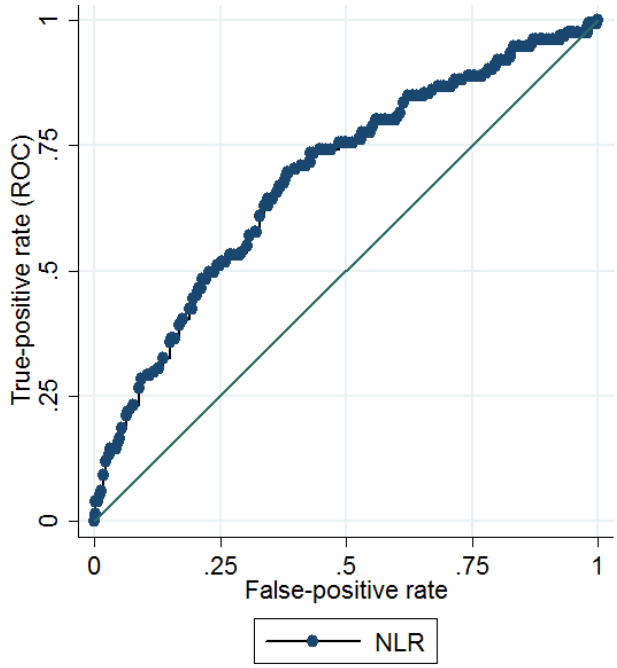

Figure 4. The receiver operating characteristic (ROC) curve of NLR for mortality of COVID-19. According to the ROC curve, the optimal cut-off point was equal to 4.27 with a sensitivity of 70.20% and a specificity of 60.22%

Discussion

The present study was conducted to provide evidence on NLR utility for the prediction of COVID-19 patient's situations. Based on our analyses, first-day NLR was independently associated with death and ICU admission. However, no significant relation with prolonged hospitalization was seen. As a result, the optimal cut-off point of first-day NLR for mortality prediction was 4.27.

Finding easy access, low-cost tests on the first admission day would be valuable. Therefore, high-risk patients would be found earlier, and their death can be prevented by using aggressive treatment. The complete blood count (CBC) test can be a nominate (25); since it reveals many markers like neutrophil count and lymphocyte count.

Studies have previously shown that NLR was associated with the prognosis of malignancy, bacteraemia, trauma, pancreatitis, and colitis (26-29). We conducted this study to investigate the association of the NLR level of COVID-19 patients at the time of admission with mortality, ICU admission, and prolonged hospitalization, hoping to point at high-risk patients and admit and treat them as soon as possible.

Although the relationship between the NLR and the severity of COVID-19 is relatively understood by scientific society, its efficacy and optimal cut-off are still under debate (25). Therefore, this study aimed to provide more evidence on this issue.

Based on the analyses, initial NLR was independently associated with mortality and ICU admission, which shows that high NLR means neutrophilia and/or lymphopenia leads the patient's situation to deterioration (30). This finding is in line with previous findings (31,32).

Two reasons have been assumed for the lymphopenia in severe patients; first, it is believed that the quantity of virus is high in these patients, and therefore, the virus directly invades to T lymphocytes (14,33); the second assumption is that lymphocytes show ACE receptors in their surface which is targeted by a cytokine storm happening in COVID-19 infection (34,35).

Some mechanisms can explain the association between NLR and death. While the lymphocyte count was low, the T-cells' response to infection would be insufficient, and thereby, the patients' prognosis would be poor. Also, high neutrophil means bacterial infection or other conditions, such as inflammation or malignancy, are present, so the patients' immune defence would be inadequate. Sometimes, the neutrophil count increases in COVID-19 due to concomitant bacterial infection or previous inflammatory situations.

To our knowledge, few investigations have been done for identifying an optimal cut-off of NLR for mortality. Former investigations for setting a cut-off proposed a broad spectrum from 3 to 6 so far (3,13,36-39). The present study suggests an optimal cut-off point of 4.27; however, considering the sample size for calculating this cut-off (963 patients), it may not be as accurate as possible.

According to the current analyses, an initial NLR ≥4.27 predicts death with a sensitivity of 70.2% and a specificity of 60.2%. Although this optimal cut-off needs curating by further researches, this range of sensitivity and specificity may imply the initial NLR's potential for being used in planning treatment at the time of admission.

Kaplan-Meier survival curves indicated that patients with higher NLR had a lower chance of survival. This finding is compatible with former investigations (38,40).

The suggested role of initial NLR in COVID-19 prognosis is consistent with the findings by Tanboga *et al*., which was based on a multivariable study of COVID-19 patients in Turkey and tried to propose a model for the prediction of outcome. The mentioned study found initial NLR as one of the strongest predictors of 30- day mortality and reported a range of 1.53 to 4.03 for initial NLR as baseline characteristics for hospitalized COVID-19 patients (15).

It seems that NLR can be a precious mediator in predicting the COVID-19 patients' mortality, which can be used for starting aggressive treatment for them at the beginning of hospitalization in order to decrease mortality (13).

Despite all efforts, this study had some limitations too. Using electronic medical records, which were not initially designed for research purposes, might have caused defections in data; therefore, conducting a prospective cohort can be more precise. Besides, only initial NLR is studied in this project, so investigating NLR changes may be helpful. To determine a cut-off point for NLR, broader investigations are needed, especially multi-center or even multi-country ones. It should be mentioned that despite the existence of molecular testing as a gold standard, false negatives intended to be covered by including patients whose chest CT imaging complied with COVID-19 infection. In addition, some other clinical data, such as the presence of pneumonia, oxygen demand, need for mechanical ventilation, and severity of disease was not available.

Initial NLR can predict mortality and ICU admission in COVID-19 patients. Further investigations for curating the calculated cut-off can propose initial NLR as an indicator of poor prognosis. Considering the CBC test's cost-effectiveness and availability, NLR can be a proper measurement at patients' admission to guide their treatment plan.

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