ORIGINAL ARTICLE

Predictive Value of Neutrophil-to-Lymphocyte Ratio at Admission for Chest X-Ray Progression in Hospitalized COVID-19 Patients

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Objective: Previous studies focused on using the neutrophil-to-lymphocyte ratio (NLR) to monitor COVID-19 patients as an early warning signal of severe COVID-19 infection. Results showed that NLR could also be used as a prognostic factor. In the present study, the role of NLR in predicting chest X-ray (CXR) progression in hospitalized COVID-19 patients was investigated.

Materials and Methods: The present study was an ambispective observational cohort study that included COVID-19 patients admitted to the isolation ward and COVID-19 intensive care unit between July and September 2021 in Buddhasothorn Hospital, Chachoengsao, Thailand. NLR and demographic findings were analyzed.

Results: Medical details of 564 patients were retrospectively analyzed using 3.24 as the cut-off value of the maximum Youden index to classify a high NLR group and a low NLR group. The estimated cumulative hazard function for CXR progression in the high NLR group was statistically significant, (HR 1.31, 95% CI 1.02 to 1.68, p=0.031). Univariate analysis suggested that high NLR value and three or more clinical risk factors (age 60 years or older, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, cirrhosis, stroke, obesity, and immunocompromised) were associated with CXR progression, while multivariate analysis determined high NLR as an independent predictive marker for COVID-19 CXR progression (aOR 1.54, 95% CI 1.06 to 2.23, p=0.022). Using NLR along with pre-existing comorbidity risk factors significantly increased the predictive value for COVID-19 CXR progression (area under the ROC curve 0.565, p=0.017).

Conclusion: High NLR at the time of hospitalization was identified as a simple predictor for COVID-19 CXR progression requiring close monitoring.

Keywords: Neutrophil-to-lymphocyte ratio (NLR); COVID-19; Disease progression; Predictive factor; Hospitalization

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Coronavirus disease 2019 (COVID-19) mainly affects the respiratory system by inducing the immune response system to form pro-inflammatory cytokines and chemokines, consisting of interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), finally causing multiorgan injury, particularly pneumonia and acute fibrinous and organizing pneumonia (AFOP)[1,2]. However, disease progression occurs only in some COVID-19 infected patients. Therefore, clinical factors and any biomarkers that can help to predict or monitor such conditions require further study.

The neutrophil-to-lymphocyte ratio (NLR) is a systemic inflammation biomarker that can be easily obtained from a peripheral blood sample and can be used to predict treatment outcomes in various conditions such as sepsis, cardiovascular disease, and survival prognosis in cancer[3-5].

Disease progression in COVID-19 patients has been linked to the immune response system, with higher neutrophils during the first five days of infection causing lung neutrophil infiltration and resulting in inflammation[6]. The NLR biomarker shows higher neutrophils and responsiveness to the immune response system.

Previous studies focused on using NLR to monitor COVID-19 patients as an early warning signal of severe COVID-19 infection. Results showed that NLR could be used as a prognostic factor for COVID-19 infection severity but cut-off values of

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NLR were different[7,8].

Factors affecting prognosis of disease progression in COVID-19 patients are not sufficiently precise, and the evidence suggests that NLR is associated with worse disease progression. Here, the NLR was assessed as a predictive marker for disease progression using chest radiography (CXR) to identify pneumonia in hospitalized COVID-19 patients and determine proper cut-off points.

Materials and Methods

The present study was an objective prognostic research based on an ambispective observational cohort study.

Patient selection and data collection

General data as e-medical records were collected for patients diagnosed with mild COVID-19 and severe risk factors who were receiving treatment in the negative pressure isolation ward and COVID-19 intensive care unit at Buddhasothorn Hospital, the Regional Tertiary Care Hospital in Chachoengsao Province, Thailand between July and September 2021. Clear guidelines were followed on treatment, monitoring laboratory test results, and CXR. Inclusion criteria were 1) patients aged 18 years or older and 2) patients with clinical history of underlying disease, laboratory test, and CXR. Exclusion criteria were patients with incomplete or missing data, patients who had received the corticosteroid, granulocyte colony-stimulating factor, or chemotherapy within 14 days before hospitalization.

The NLR was calculated using the simple formula of absolute number of neutrophils divided by absolute number of lymphocytes.

Classifying COVID-19 severity

Following the NIH guidance, patients were classified as having mild, moderate, severe, and critical COVID-19 as per the following criteria.

Asymptomatic for patients who testing positive for SARS-CoV-2 but did not have symptoms attributable to COVID-19.

Mild illness for patients who had any of the various signs and symptoms of COVID-19, such as fever, cough, sore throat, loss of taste and smell, malaise, headache, nausea, vomiting, diarrhea, but did not have shortness of breath, dyspnea, or abnormal chest radiographs.

Moderate illness for patients who had evidence of lower respiratory tract infection on clinical evaluation or imaging and had an oxygen saturation (SpO_2) of 94% or more on room air.

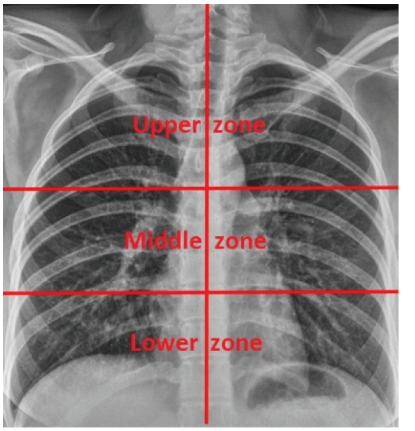

Figure 1. Division of lungs into three zones on frontal chest radiograph (adapted from Litmanovich et al.[9]).

Severe illness for patients with an SpO_2 of less than 94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) of less than 0 mmHg, a respiratory rate of more than 30 breaths per minute, or pulmonary infiltrates greater than 50%.

Critical illness for patients with respiratory failure, septic shock, or multiple organ dysfunction.

Hospitalization criteria, including patients with moderate-to-critical illness and mild illness, and higher risk patients with certain underlying comorbidities that had a higher risk of progressing to severe COVID-19. These comorbidities included being aged 60 years or older, having cardiovascular disease, stroke, chronic lung disease, diabetes mellitus, obesity, chronic kidney disease, cirrhosis, or immunocompromised.

Definition of disease progression

To facilitate monitoring of radiographic lung changes, the authors used the six-point radiographic severity score. As shown in Figure 1, the score was designed to be divided into three zones per lung or six zones in total. The upper zone extended from the apices to the upper part of the hilum. The middle zone extended across the space between the upper and lower hilum margins. The lower zone extended from the inferior hilar margins to the costophrenic angle.

A severity score was calculated by adjusting and simplifying the chest radiography findings from COVID-19 Pneumonia and Suggested Reporting Language[9]. Each chest radiograph was assigned a score of 0 to 3 depending on the extent of involvement by consolidation or ground-glass opacities with 0 for

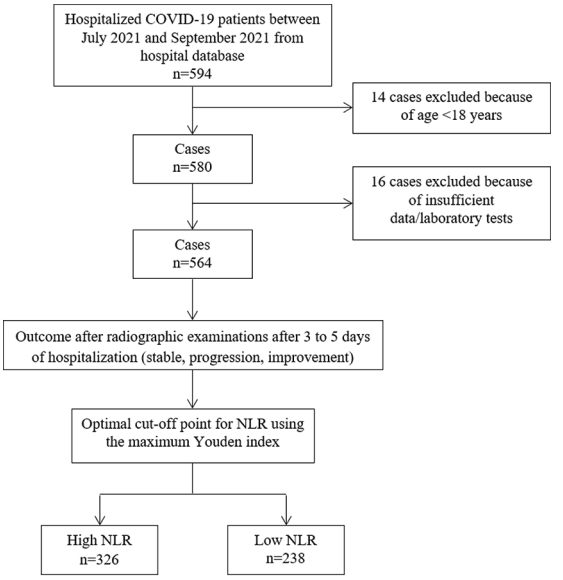

Figure 2. Patient selection flow chart.

no involvement, 1 for opacities in one or two lung zones, 2 for opacities in three or four lung zones, and 3 for opacities in more than four lung zones[10,11].

On follow-up radiographs after three to five days of hospitalization, the degree of lung disease could be further specified such as stable, increased, or decreased severity. Definition of stable severity means that the radiological severity had remained stable, increased severity meant the radiological severity had increased, and decreasing severity meant the radiological severity had decreased.

The present retrospective chart review study was conducted in compliance with the revised principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board (number BSH-IRB 030/2564), which determined that formal patient consent was not required.

Statistical analyses

The Youden index was estimated to select the optimal cut-off value for NLR. The odds ratio (OR) with a 95% confidence interval (CI) was used to estimate the prediction value of NLR for predicted CXR progression. Univariate and multivariate logistic regression analyses were performed to identify the independent factors for predicting CXR progression in patients with moderate to severe delta variant COVID-19 infection. The discriminative ability of prediction was assessed by the area under the receiver operating characteristic curve (ROC curve).

Table 1. Clinical characteristics of hospitalized COVID-19 patients (n=564)

Variables	n (%)
Sex	
Male	218 (33.87)
Female	346 (66.13)
Risk factors	
No	191 (33.87)
Yes	373 (66.13)
Age ≥60 years	267 (47.34)
Diabetes mellitus	114 (20.21)
Chronic obstructive pulmonary disease	4 (0.71)
Chronic kidney disease	135 (23.94)
Cirrhosis	2 (0.35)
Stroke	17 (3.01)
Obesity (BW >90 kg)	16 (2.84)
Immunocompromised	3 (0.53)
Baseline chest radiography at admission	
Normal	61 (10.82)
Mild pneumonia	175 (31.03)
Moderate pneumonia	145 (25.71)
Severe pneumonia	183 (32.45)
Initial diagnosis	
Symptomatic COVID-19 without risk factors	30 (5.32)
Symptomatic COVID-19 with risk factors	31 (5.50)
COVID-19 pneumonia	503 (89.18)
Early favipiravia treatment	
No	44 (7.82)
Yes	519 (92.18)
Ventilator	
No	492 (87.70)
Yes	69 (12.30)

BW=body weight

All statistical tests were two-sided, and p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using Stata Statistical Software, version 16 (StataCorp LLC, College Station, TX, USA).

Results

Patient characteristics

Five hundred sixty-five confirmed hospitalized cases of COVID-19 were eligible for analyses. The flowchart for patient selection is shown in Figure 2. Average age of the patients was 40.25±17.11 years, with 218 males and 346 females. Median NLR was 4, the interquartile range (IQR) was 2.07 to 7.76. Five hundred three (89.18%) had pneumonia at the beginning of hospitalization, as shown in Table 1. When chest radiographs were assessed after three

to five days of hospitalization, chest radiographs worsened in 290 patients, remained stable in 148, and improved in 126 patients.

Optimal cut-off values for NLR

The optimal cut-off point using the maximum Youden index from the ROC curve of the NLR for predicting CXR progression was 3.24, with sensitivity 55.5% (95% CI 49.9 to 61.0), specificity 54.2% (95% CI 47.6 to 60.7), positive predictive value (PPV) 62.4%, negative predictive value (NPV) 47.1%, positive likelihood ratio (LR+) 1.21, negative likelihood ratio (LR–) 0.82, and area under the curve (AUC) 0.548 (95% CI 0.51 to 0.59). A graphic of ROC curves is presented in Figure 3. According to the optimal cut-off value of NLR, the authors divided 238 patients with NLR of less than 3.24 into the low NLR group and 326 patients with NLR of 3.24 or more into the high NLR group. The estimated cumulative hazard function for CXR progression was statistically significantly different between the groups (HR 1.31, 95% CI 1.02 to 1.68, p=0.031) (Figure 4).

Correlation between NLR variable and disease progression

In the univariable regression analysis, high NLR (≥3.24) and clinical risk factors (≥3) were associated with disease progression. High NLR (≥3.24), clinical risk factors (≥3), and mild pneumonia on hospitalization were significantly associated with an independent predictive factor by multivariable exploratory data analysis (Table 2). Multivariable regression analysis identified high NLR as a strong independent factor for CXR progression prediction in hospitalized COVID-19 patients (aOR 1.54, 95% CI 1.06 to 2.23, p=0.022).

Prediction value of NLR for CXR progression

When an NLR cut-off point of 3.24 or higher was used to predict CXR progression, the area under the ROC curve (AUROC) was 0.548, as shown in Figure 3. In a value-added analysis of NLR plus three or more clinical risk factors to predict CXR progression, the AUROC was 0.565, 95% CI 0.51 to 0.59 sensitivity 57.1% (95% CI 50.6 to 63.4), specificity 52.6% (95% CI 47.0 to 58.2), PPV 47.2%, NPV 62.3%, LR+ 1.21, LR– 0.82 compared with using multiple clinical risk factors alone, which gave an AUROC of 0.518, as shown in Figure 5. The use of NLR along with pre-existing comorbidity risk factors significantly increased the value of prediction for CXR progression of COVID-19, p=0.017.

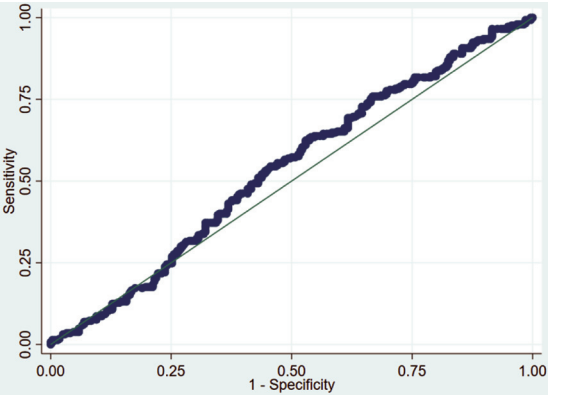

Figure 3. The optimal cut-off point of NLR was 3.24. The area under the ROC curve was 0.548, 95% CI 0.51 to 0.59, sensitivity 55.5% (95% CI 49.9 to 61.0), specificity 54.2% (95% CI 47.6 to 60.7), positive predictive value (PPV) 62.4%, negative predictive value (NPV) 47.1%, positive likelihood ratio (LR+) 1.21, negative likelihood ratio (LR–) 0.82.

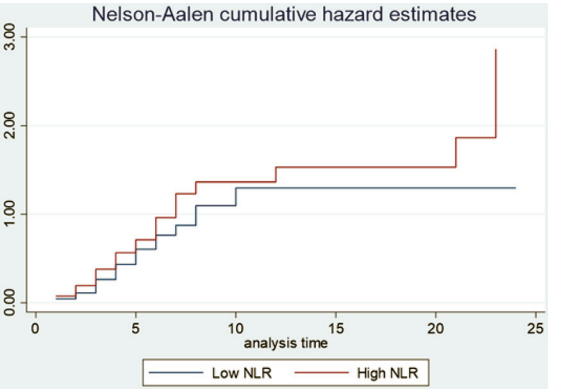

Figure 4. Cumulative hazard curve for CXR progression in COVID-19 patients between the high NLR group and the low NLR group.

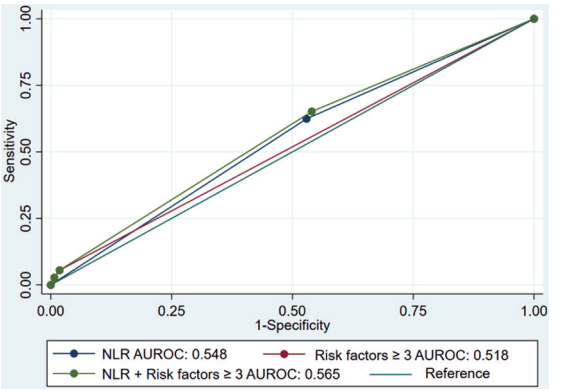

Figure 5. Comparison of ROC curve and AUC values between NLR, multiple risk factors (≥3), and combined NLR and multiple risk factors for predicting CXR progression in COVID-19 patients.

Table 2. Results of univariable and multivariable logistic regression analyses of potential variables as independent predictors of CXR progression in COVID-19 patients

Variables	Univariable analyses			Multivariable analyses		
	uOR	95% CI	p-value	aOR	95% CI	p-value
NLR						
Low (<3.24)	1	(omitted)		1	(omitted)	
High (≥3.24)	1.48	1.06 to 2.07	0.023*	1.54	1.06 to 2.23	0.022*
Sex						
Male	1	(omitted)		1	(omitted)	
Female	0.79	0.56 to 1.11	0.172	0.82	0.58 to 1.17	0.274
Age (in years)						
<60	1	(omitted)		1	(omitted)	
≥60	1.06	0.76 to 1.48	0.711	0.76	0.47 to 1.21	0.248
Risk factors						
No	1	(omitted)		1	(omitted)	
Risk 1	1.03	0.69 to 1.52	0.894	1.12	0.68 to 1.82	0.663
Risk 2	1.47	0.95 to 2.27	0.082	1.67		0.096
Risk ≥3	3.52	1.24 to 9.98	0.018*	4.71	1.50 to 14.78	0.008*
Chest radiography						
Normal	1	(omitted)		1	(omitted)	
Mild pneumonia	1.71	0.95 to 3.09	0.073	1.94	1.06 to 3.57	0.033*
Moderate pneumonia	1.66	0.90 to 3.03	0.101	1.65	0.88 to 3.08	0.116
Severe pneumonia	1.19	0.66 to 2.14	0.553	1.12	0.60 to 2.07	0.728

uOR=unadjusted odds ratio; aOR=adjusted odds ratio; CI=confidence interval; NLR=neutrophil-to-lymphocyte ratio

* Statistically significant p-values

Discussion

Results revealed that high NLR of 3.24 or more was an independent predictive factor for CXR progression according to the multivariable regression analysis (aOR 1.54, 95% CI 1.06 to 2.23, p=0.022). Moreover, patients with three or more comorbidity risk factors and mild pneumonia since hospitalization were also related to CXR progression.

Previous studies found dynamic changes in hematologic and inflammatory biomarkers in the body during the first five days of COVID-19 infection, particularly in patients with severe symptoms leading to death[12]. This group of patients recorded high leukocytes, neutrophils, NLR, C-reactive protein, procalcitonin (PCT), IL-6, prothrombin time, D-dimer, serum amyloid A (SAA), and ferritin, causing higher systemic inflammatory response resulted in severe disease progression[13]. One of the most studied biomarkers was NLR[14,15].

The NLR is a simple biomarker obtained by calculating white blood cell count levels. The NLR is calculated using a simple formula of the absolute number of neutrophils divided by the absolute number of lymphocytes. The NLR in peripheral blood reflects the balance between systemic inflammation and immunity[3,16]. NLR levels have been widely investigated in conditions such as solid malignancies including hematological malignancies, cardiovascular diseases, and systemic infectious diseases. They are emerging as a prognostic biomarker in diseases. Higher NLR levels have been associated with more severe forms of illness with the worst prognosis[5,17,18]. NLR is a prognostic indicator related to the severity of COVID-19[19,20]. A study on meta-analysis confirmed that NLR could be used for critical illness prediction in COVID-19 patients[21,22].

Previous studies predicted factors for COVID-19 disease progression such as elderly patients aged 65 years or older with blood SpO_2, C-reactive protein, prothrombin time and chronic obstructive pulmonary disease[23]. However, most developing countries still use clinical factors to classify patient groups at risk of severe COVID-19 prognosis. These include patients aged 60 years or older with cardiovascular disease, chronic lung disease, diabetes mellitus, obesity, sickle cell disease, chronic kidney disease, being a transplant recipient and receiving immunosuppressive therapy[24]. Limited studies exist on NLR as a predictive factor.

Therefore, here, the NLR value was studied as an

independent predictive marker for CXR progression in hospitalized COVID-19 patients. However, limitations were found. Using NLR as the only factor had low predictive ability, with AUROC 0.548. When used with other clinical risk factors to predict CXR progression, the AUROC value increased to 0.565. This was significantly higher, but prediction accuracy was still low. Therefore, further studies on other factors are required to support the prediction of clinical progressions such as blood SpO_2 change after exercise and C-reactive protein for precise prediction/prognosis of CXR progression.

Conclusion

The NLR value can be used as an early marker for predicting COVID-19 CXR progression as an independent predictive factor. However, using NLR alone cannot precisely predict COVID-19 CXR progression. NLR assessment must be combined with other clinical risk factors including comorbidity diseases, blood SpO_2, and C-reactive protein. Further studies on other predictive factors are required for future utilization in patient care.

What is already known on this topic?

Pretreatment NLR levels greater than or equal to 3.24 before treatment can be used as an independent predictive marker for predicting disease progression based on chest radiography in hospitalized COVID-19 patients.

What this study adds?

According to this study, NLR is an independent predictive marker for CXR progression, when used in combination with clinical factors including patients aged 60 years or older with cardiovascular disease, chronic lung disease, diabetes mellitus, obesity, sickle cell disease, chronic kidney disease, and being a transplant recipient and receiving immunosuppressive therapy, may improve predictive accuracy.

Ethical approval

The present study protocol was approved by the Institutional Review Board of Buddhasothorn Hospital, number BSH-IRB 030/2564.

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Conflicts of interests

The authors have no conflicts of interest to declare.

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