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ORIGINAL RESEARCH

Validation of Neutrophil-to-Lymphocyte Ratio Cut-off Value Associated with High In-Hospital Mortality in COVID-19 Patients

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Introduction: The neutrophil-to-lymphocyte ratio (NLR) could be a predictive factor of severe COVID-19. However, most relevant studies are retrospective, and the optimal NLR cut-off point has not been determined. The objective of our research was identification and validation of the best NLR cut-off value on admission that could predict high in-hospital mortality in COVID-19 patients.

Methods: Medical files of all patients admitted for COVID-19 pneumonia in our dedicated COVID-units between March and April 2020 (derivation cohort) and between October and December 2020 (validation cohort) were reviewed.

Results: Two hundred ninety-nine patients were included in the study (198 in the derivation and 101 in the validation cohort, respectively). Youden's J statistic in the derivation cohort determined the optimal cut-off value for the performance of NLR at admission to predict mortality in hospitalized patients with COVID-19. The NLR cut-off value of 5.94 had a sensitivity of 62% and specificity of 64%. In ROC curve analysis, the AUC was 0.665 [95% CI 0.530–0.801, p= 0.025]. In the validation cohort, the best predictive cut-off value of NLR was 6.4, which corresponded to a sensitivity of 63% and a specificity of 64% with AUC 0.766 [95% CI 0.651–0.881, p <0.001]. When the NLR cut-off value of 5.94 was applied in the validation cohort, there was no significant difference in death and survival in comparison with the derivation NLR cut-off. Net reclassification improvement (NRI) analysis showed no significant classification change in outcome between both NLR cut-off values (NRI:0.012, p=0.31).

Conclusion: In prospective analysis, an NLR value of 5.94 predicted high in-hospital mortality upon admission in patients hospitalized for COVID-19 pneumonia.

Keywords: neutrophil-to-lymphocyte ratio, coronavirus disease, SARS-CoV-2 infection, COVID-19, risk factors, laboratory markers

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, secondary to SARS-CoV-2 infection, is a serious disease worldwide.[1] Risk factors for severe COVID-19 are age, male sex, genetic variants (in Eurasians),[2] inborn errors, or auto-antibodies interfering with interferon or immunity[3] and chronic diseases such as high blood pressure, cardiovascular disease, and diabetes.[4] While research for effective treatment of COVD-19 and large-scale vaccination campaigns are ongoing, identifying biomarkers on admission that could predict in-hospital mortality remain important. Abnormal laboratory markers on admission that have been associated with

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mortality[1,5,6] are elevated serum levels of creatinine, D-dimer, troponin I, lactate dehydrogenase (LDH) and IL-6 as well as thrombocytopenia. Many prognostic scores have been developed[7–9] and differ in their predicted outcome measure and clinical parameters.[7]

Recently, Knight et al[8] developed the 4 C Mortality Score. The score ranges from 0 to 21 points and includes the usual clinical and biological variables, such as age, sex, number of comorbidities, breathing rate, peripheral oxygen saturation, Glasgow coma scale, urea, and CRP levels. A score of ≥15 had a 62% mortality risk compared with 1% mortality risk for those with a score of ≤ 3, which is better than previously developed scores (ROC analysis with AUC range 0.61–0.76). Many studies have reported that the neutrophil-to-lymphocyte ratio (NLR) can predict severe disease.[9–14] However, most of the studies were retrospective, and the optimal NLR cut-off point is lacking.

The objective of our research was to identify and validate the best NLR cut-off value on admission which could predict high in-hospital mortality in COVID-19 patients.

Methods

Setting and Patients

The study was conducted in one of the largest teaching hospitals in Belgium. Medical files of patients with COVID-19 pneumonia admitted to our dedicated COVID-19 units were reviewed. Patients admitted between March 2020 and April 2020 (derivation cohort) were retrospectively analyzed to identify the NLR cut-off point on admission that enabled mortality prediction. We then prospectively included 101 patients between 01 October 2020 and 25 December 2020 (validation cohort) to validate the NLR cut-off point. Only patients with a positive RT-PCR nasopharyngeal swab were included. The definition of severe COVID-19 was (≥1 positive criteria): (1) respiration rate ≥30 breaths per minute; (2) mean oxygen saturation <94% while breathing room air; (3) arterial blood oxygen partial pressure/oxygen concentration ≤ 300 mm Hg (1 mm Hg = 0.133kPa). Patients were excluded if <18 years old, undergoing palliative care, pregnant, or under chemotherapy for solid cancer or hematological disease (lymphoma, leukemia, myeloma).

Ethical Issues

The institutional ethical board approved the study (CEHF 2020/06AVR/201, Comité d'Ethique Hospitalo-Facultaire, Cliniques Universitaires Saint-Luc). Since the study was not an interventional study and that we analysed routine laboratory tests, which were already performed in all patients, informed consent was not necessary according to Belgian and local ethics law. The study was performed in accordance with the principles stated in the Declaration of Helsinki, and confidentiality of patients was guaranteed.

Data Analysis

We used our institutional database to collect the following data of all hospitalized COVID-19 patients: Demographic characteristics (age, sex, ethnicity); tobacco use; symptoms; clinical parameters; laboratory data (neutrophil count, lymphocyte count, eosinophil count, NLR, LDH, renal function, uric acid, troponin, C-reactive protein, ferritin, and D-dimer); treatment against SARS-CoV-2 and results of chest CT scan. Blood processing machines (Cobas® 8100 [Roche] and XN9000 [Sysmex]) were used to enumerate neutrophils and lymphocytes in the blood. Neutrophil-to-lymphocyte index was obtained by machine-derived cell differentials (neutrophil count divided by lymphocyte count). Chest CT images were classified as 1) compatible or not compatible with COVID-19 pneumonia; 2) the percent of lung involved (<10%, 10–25%, 25–50%, or >50%), based on visual assessment of radiological lung lesions. Risk factors associated with severe COVID-19, such as age, malignancy (without chemotherapy), cardiac disease, high blood pressure, diabetes, COPD, liver disease, the need for oxygen supplementation or ventilation support, admission to the intensive care unit (ICU), death, and length of stay in the dedicated COVID-19 unit were collected.

Statistical Analysis

Continuous variables were expressed as mean and standard deviations and categorical variables as counts and percentages. Categorical and continuous variables were compared with the Chi-squared test and the unpaired Student's *t*-test, respectively. Youden's J statistics was used in both cohorts to identify the best predictive cut-off values of NLR on admission associated with high in-hospital mortality. Net reclassification improvement analysis was calculated to assess whether the NLR cut-off evaluated in both cohorts led to classification changes. Receiver-operating characteristic (ROC) curves were computed to measure the discrimination performance of cut-off values. The odds ratio (OR) of NLR for predicting mortality was calculated with univariate binary logistic regression.

All analyses were conducted with SPSS 27 software (IBM SPSS Statistics for Windows, Version 27.0, Armonk, NY: IBM Corp). All tests were 2-sided with 0.05 as the significance threshold.

Results

Clinical Characteristics and Outcome

Demographics and clinical characteristics of patients included in the validation and derivation cohorts are summarized in Table 1. Age, comorbidity, and severity of the diseases were similar between the two cohorts.

ROC Curve and Youden Index Analysis in the Derivation (n=198) and Validation (n=101) Cohorts

In the derivation cohort, the best predictive cut-off value of NLR on admission was 5.94, which was associated with 62% sensitivity and 64% specificity. Discrimination performances by ROC analysis (Figure 1A) for predicting mortality in hospitalized patients with COVID-19 had an AUC of 0.665 [95% CI 0.530–0.801, p = 0.025]. In the validation cohort, the optimal cut-off value of NLR was slightly different (6.4), with corresponding sensitivity of 63% and specificity of 64%. ROC analysis (Figure 1B) showed an AUC of 0.766 [95% CI 0.651–0.881, p <0.001]. When the NLR cut-off value of 5.94 was applied in the validation cohort, no significant differences in death and survival between the 2 cut-off values were found (Table 2). Net reclassification improvement (NRI) analysis confirmed that there were no statistically significant classification changes in terms of outcome, by using both NLR cut off values (NRI: 0.012, p= 0.31). Univariate analysis showed that the NLR cut-off value of 5.94 was associated with an odds ratio of 3.9 for death (CI 95% 1.13–11.50, p=0.012).

Discussion

The main outcome of this study was the identification of the neutrophil-to-lymphocyte ratio (NLR) cut-off point on admission that predicted high in-hospital mortality from COVID-19 pneumonia; the cut-off value of 5.94 was associated with an odds ratio of 3.9 for death. Interest in NLR is keen because it is a simple and cheap biomarker. While many prognostic tools have been developed for COVID-19, the simplicity of the NLR likely will make it useful in a broad range of health-care systems, especially in limited-resource settings.

Table 1 Clinical Characteristics of Patients with COVID-19

Characteristics	Derivation Cohort (N=198)	Validation Cohort (N=101)	P value
Sexe (Male)	110 (55%)	65 (64%)	0.14
Mean Age	64.4 [14]	62.3 [17.2]	0.269
BMI (kg/m^2)	28 [5]	27 [5]	0.444
Smoking	8 (4%)	2 (2%)	0.35
Mean SpO2*	90% [4.6]	89% [4.5]	0.004
Nbr of patients with OT	179 (91%)	99 (98%)	0.02
Mechanical and non-mechanical respiratory support			
HFNC	29 (15%)	16 (15.8%)	0.78
Oxygen mask	87 (44%)	55 (54.5%)	0.09
CPAP	56 (28%)	43 (42%)	0.13
Invasive mechanical ventilation	18 (9%)	8 (7.9%)	0.73
Co-morbidities			
Cardiovascular disease	107 (54%)	45 (44.6%)	0.12
Hypertension	101 (51%)	52 (51.5%)	0.94
Chronic pulmonary disease	33 (17%)	10 (9.9%)	0.11
Diabetes	49 (25%)	22 (21.8%)	0.6
Immunosuppression	24 (12%)	18 (17.8%)	0.18
Chronic liver disease	10 (5%)	2 (2%)	0.2
Chronic kidney disease	36 (18%)	16 (15.8%)	0.54
Malignancy	10 (5%)	6 (5.9%)	0.75
Biological data			
CRP on admission (mg/dl)	103.4 [81.7]	100 [74.8]	0.735
WBC count on admission	6.7 [3.3]	7 [3.7]	0.431
Absolute Neutrophil Count on admission (x10 ^{3}/mm^3)	5.13 [2.99]	5.5 [3.3]	0.398
NLR on admission	7 [7.4]	7.3 [6.1]	0.767
Eosinophil count on admission (x10 ^{3}/mm^3)	0.02 (0.04)	0.02 (0.05)	0.930
LDH (UI/L)	385 [189]	369 [136]	0.445
AST (UI/L)	54 [81]	43 [26]	0.195
ALT (UI/L)	39 [74]	36 [31]	0.696
D-Dimer (ng/mL)	2634 [4077]	1926 [3349]	0.177
Creatinine (mg/dl)	1.4 [1.6]	1.4 [3]	0.867
Troponin T (ng/L)	31.2 [69.1]	15.2 [19.2]	
Lung CT scan	188 (95%)	80 (79.2%)	0.001
Stratification of lung lesions on CT scan			
<10%	15 (7.6%)	7 (6.9%)	0.2

(*Continued*)

Table 1 (Continued).

Characteristics	Derivation Cohort (N=198)	Validation Cohort (N=101)	P value
10–25%	90 (45.5%)	28 (27.7%)	
25–50%	53 (26.8%)	25 (24.8%)	
>50%	30 (15.2%)	20 (19.8%)	
Outcome			
Overall death	29 (15%)	19 (18.8%)	0.35
ICU admission	37 (19%)	16 (15.8%)	0.54
Death in ICU	11 (6%)	6 (5.9%)	0.9
Treatment			
HCQ	144 (72.7%)	/	
HCQ with AZT	18 (9.1%)	/	
HCQ combined with CS	19 (9.6%)	/	
HCQ with AZT and CS	17 (8.6%)	/	
Dexamethasone	/	101 (100%)	

Notes: *When breathing ambient air. Data are mean (SD), Interquartile range [IQR] or percentage (%).

Abbreviations: OT, oxygen therapy; HCQ, hydroxychloroquine; AZT, azithromycin; CS, corticosteroids; HFNC, high Flow Nasal Cannula; NLR, neutrophil to lymphocyte ratio; CPAP, continuous positive airway pressure; CRP, C-reactive protein, ICU: intensive care unit.

Increased NLR is a risk factor for mortality in various diseases, such as hip fractures, infection, malignant diseases, acute myocardial ischemia, and polymyositis.[15–18] Several studies have found that that NLR is associated with progression and mortality of COVID-19.[19–24] However, most of these studies were retrospective, and prospective studies have been needed. Li et al[10] included 19 studies in their meta-analysis, and only one was prospective. Li et al[25] found, in a meta-analysis including 34 studies (25,074 COVID-19 patients) that high NLR was an independent risk factor for high mortality. Thirteen studies (1579 patients) found that NLR was predictive of disease severity with an AUC 0.85 (95% CI 0.81–0.88). Ten studies (2967 patients) reported that NLR was predictive of mortality, with 83% sensitivity and specificity. In their subgroup analysis, 10 studies showed that an NLR cut-off value ≥ 6.5 and < 6.5 were predictive of mortality with AUC 0.92 (95% CI 0.89–0.94) and 0.84 (95% CI 0.80–0.87), respectively. This cut-off value is in line with our NLR 5.94 and 6.4 in the derivation and validation cohort, respectively. Compared with the results of the meta-analysis of Hariyanto et al,[26] NLR is as efficient as C-reactive protein, D-dimer, LDH, and procalcitonin in predicting severe outcome on admission in patients with COVID-19.

The mechanism by which NLR is associated with poor outcomes was first proposed by Zahorec et al[27] They showed that in stress, values of inflammatory cytokines and neutrophils are increased, which may induce a decrease in lymphocyte counts and apoptosis. Since lymphocytes are involved in the regulation of the inflammatory response, the decrease in their numbers may be

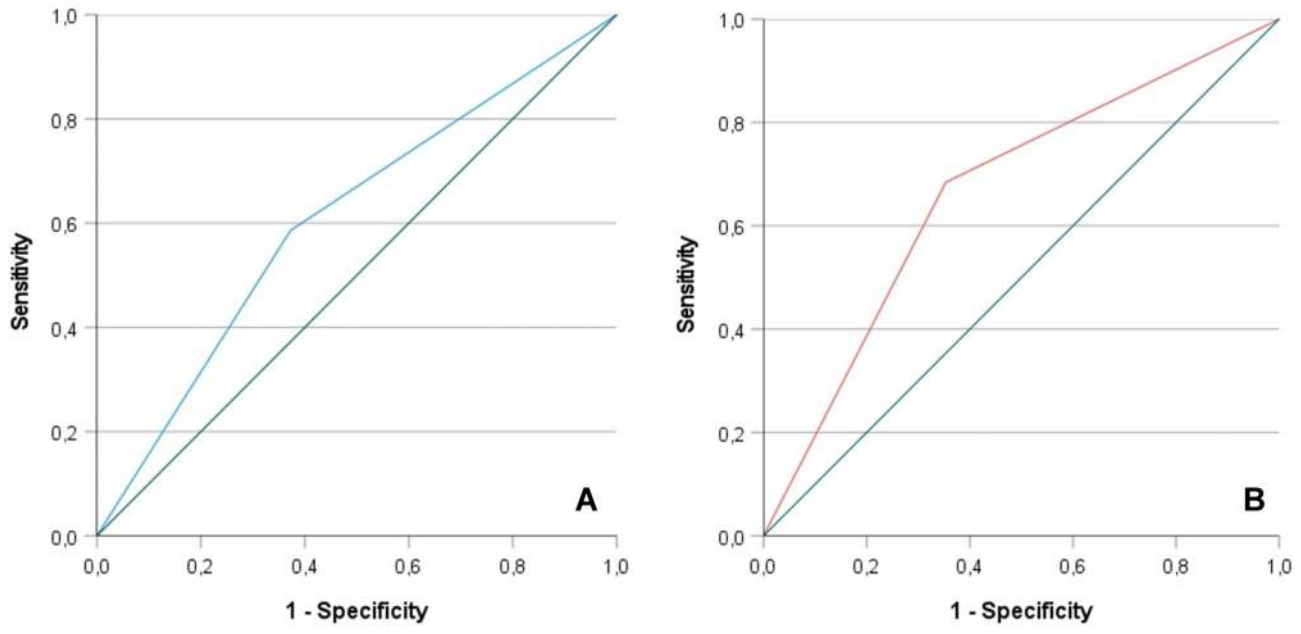

Figure 1 Receiver-operating characteristic (ROC) curves showing the discrimination performance of NLR cut off values in the derivation (1**A**) and validation (1**B**) cohort.

Table 2 Overall Death According to Different NLR Cut-off Value in the Validation Cohort and Evaluation by Net Reclassification Improvement

NLR	Death	Alive	p value	NRI
NLR <5.94	6 (32%)	53 (65%)	0.008	0.012 (p value =0.31)
NLR >5.94	13 (68%)	29 (35%)		
NLR <6.4	6 (32%)	54 (67%)	0.006	
NLR >6.4	13 (68%)	28 (34%)		

Abbreviations: NRI, net reclassification improvement; NLR, neutrophil to lymphocyte ratio.

harmful and give rise to a high inflammatory state.[28] COVID-19 infection is characterized by lymphopenia and high cytokine production, such as in haemophagocytic lymphohistiocytosis, with increased levels of IL-1, IL-2, IL-6, IL-7, and tumour necrosis factor-α.[29] Biomarkers such as IL-6 and IL-1 are associated with poor outcome, but since these biomarkers are not widely available, others are needed. The NLR is an easily calculated blood test that can help to quickly identify patients at high risk of death and thereby improve their management.

Several other biomarkers (COVID-GRAM, NEWS 2, and 4C mortality score) have been proposed to help identify patients who may have life-threatening COVID disease.[8,12,30] The COVID-GRAM, constructed by Liang et al,[12] is based on 10 variables, with NLR being one of its components. However, many parameters such as creatinine, D-dimer, ferritin, and sex that are associated with high mortality are not included in the COVID-GRAM. In a previous study,[9] we retrospectively validated COVID-GRAM and found that NLR on admission and day 3 may predict patients at risk of critical disease as effectively as does COVID-GRAM. NEWS2 score seems to be significantly associated with intubation, whereas 4C mortality score was predictive of mortality.[8,30,31] Recently, Yildiz et al[31] prospectively validated these scores in a cohort of 114 patients; 4C mortality score had the highest discrimination for mortality prediction. NEWS2 on admission seems to be a better predictor of ICU admission than are CURB-65, COVID-GRAM, and 4C mortality score.[31] Compared with the four scores cited above, NLR on admission was also predictive of in–hospital mortality but not of ICU admission.[31]

Artificial intelligence systems have been studied to improve outcome of patients with COVID-19.[32–36] These machine-learning systems can determine the relationships between clinical data and variables associated with outcome (mortality and ICU admission) without using linear or logistic regression. Studies using machine-learning systems showed that CRP, LDH, and procalcitonin were predictors of mortality and ICU admission, whereas D-dimer, age, and lymphocytes were better predictors of mortality than were ferritin, oxygen saturation, and temperature, which were better predictors of ICU admission.[32–36] Most of the studies based on artificial systems need validation in prospective and multicentric study but seem promising. However, artificial systems should be used with caution in COVID-19 patients since they may exacerbate the health inequities already present in developing countries.[37]

Our study has limitations. 1) It is a monocentric study, and the sample size is small. Only Belgian patients are represented, so our findings need external validation with variable and larger populations. 2) Whether the NLR cut-off value can be used for more aggressive management and treatment of patients needs to be tested in multicenter, randomized, and prospective studies. 3) The effects of treatment of comorbidities associated with COVID-19 were not assessed. Drugs such as metformin, insulin, and DPP-4 inhibitors could affect survival. Several meta-analyses have studied the impact of diabetes drugs on outcome of patients infected with COVID-19.[38–40] While insulin therapy seems to be associated with poor outcome, metformin use was associated with reduced mortality in COVID-19 patients,[39] but two recent studies found that DPP-4 inhibitor use was not associated with poor outcome.[40,41]

Conclusions

In a prospective study, a neutrophil-to-lymphocyte ratio value of 5.94 was the best predictive value of in-hospital mortality for COVID-19. The neutrophil-to-lymphocyte ratio may be useful for clinicians in a broad range of health care systems, especially in limited-resource settings

where other inflammatory markers (interleukins, ferritin, and D-dimer) and CT scan are not available.

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Disclosure

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