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The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients

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ABSTRACT

Aim: To accumulate evidence that indicated the key role played by virus-triggered inflammation in the 2019-novel coronavirus disease (COVID-19) which emerged in Wuhan City and rapidly spread throughout China.
Methods: Age, neutrophil(NEU)-to-lymphocyte (LYM) ratio (NLR), lymphocyte-to-monocyte (MON) ratio, platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP) of 93 patients with laboratory confirmed COVID-19 were investigated and compared. The receiver operating characteristic curve was applied to determine the thresholds for five bio-markers, and their prognostic values were assessed via the Kaplan–Meier curve and multivariate COX regression models.
Results: The median age was 46.4 years old, and 37cases were females. A total of 27.8% of patients had been to Wuhan, and 73.1% had contacted with people from Wuhan. Fever (83.8%) and cough (70.9%) were the two most common symptoms. Elevated NLR and age were significantly associated with illness severity. The binary logistic analysis identified elevated NLR (hazard risk [HR] 2.46, 95% confidence interval [CI] 1.98–4.57) and age (HR 2.52, 95% CI 1.65–4.83) as independent factors for poor clinical outcome of COVID-19. NLR exhibited the largest area under the curve at 0.841, with the highest specificity (63.6%) and sensitivity (88%).
Conclusions: Elevated age and NLR can be considered independent biomarkers for indicating poor clinical outcomes.

1. Introduction

In early December 2019, several cases of pneumonia of unknown etiology have been reported in Wuhan, Hubei province, China [1]. On January 7, 2020, the Chinese Center for Disease Control and Prevention (CDC) has revealed a novel beta-coronavirus from the throat swab sample of a patient through high-throughput sequencing [2]. The disease resembles severe acute respiratory syndrome coronavirus (SARS-CoV) [3] and has been subsequently named the 2019-novel coronavirus disease (COVID-19) by the World Health Organization (WHO). Evidence pointing to the person-to-person transmission has occurred among close contacts in hospital and family [4,5]. Considerable efforts for reducing transmission are required to control outbreaks. Coronaviruses, such as SARS-CoV [6] and MERS-CoV [7], can cause multiple system infections in various animals and mainly induce respiratory tract infections in humans [6]. Most patients exhibited mild symptoms and partial patients exhibited worse prognosis. To date, only a few COVID-19 patients have developed into severe pneumonia, pulmonary edema, acute respiratory distress syndrome [1,7], or multiple organ failure and eventually died. Given the rapid spread and serious harm of COVID-19, it is urgent to continuously improve and enrich its clinical diagnosis and treatment research. This updated analysis identified the defining laboratory results and clinical characteristics with improved precision and also elucidated the risk factors associated with mortality.

Inflammation is caused by infectious diseases, and growing evidence supports its significant role in the progression of various viral pneumonia, including COVID-19 [8]. Severe inflammatory responses contribute to weak adaptive immune response, thereby resulting in immune response imbalance. Therefore, circulating biomarkers that can represent inflammation and immune status are potential predictors for the prognosis of COVID-19 patients [9]. Peripheral white blood cell (WBC) count, neutrophil (NEU)-to-lymphocyte (LYM) ratio (NLR), derived NLR ratio (d-NLR, neutrophil count divided by the result of WBC count minus neutrophil count), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) are indicators of the systematic inflammatory response [10] that are widely investigated as useful

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Table 1
Baseline characteristics and results of NLR, PLR, d-NLR, WBC, CRP above 93 2019-nCoV pneumonia patients.

	Total	Non-severe (n = 69)	Severe (including Critical illness) (n = 24)	Statistic test
Age (M ± SD)	46.4 ± 17.6	42.1 ± 18.6	57.9 ± 11.8	F = 4.65, P = 0.034
Sex (M/F)	56/37	38/31	18/6	χ^2 = 2.233, P = 0.135
WBC (M ± SD)	6.93 ± 3.9	6.4 ± 2.4	9.1 ± 5.6	F = 7.977, P = 0.006
LYM	1.04 ± 0.64	1.17 ± 0.63	0.65 ± 0.54	Z = −4.115, P < 0.001
NEU	5.38 ± 3.6	4.55 ± 0.21	7.73 ± 5.4	F = 13.18, P < 0.001
MON	0.43 ± 0.46	0.41 ± 0.2	0.5 ± 0.84	Z = −2.009, P = 0.045
NLR (M ± SD)	10.8 ± 15.6	4.8 ± 3.5	20.7 ± 24.1	Z = −4.798, P < 0.001
d-NLR (M ± SD)	5.07 ± 5.5	3.3 ± 1.9	9.8 ± 7.8	Z = −4.429, P < 0.001
LMR (M ± SD)	3.42 ± 4.6	4.1 ± 6.0	2.1 ± 1.6	Z = −3.306, P = 0.001
PLR (M ± SD)	255.8 ± 226.1	176.7 ± 84.2	436.5 ± 329.2	Z = −3.992, P < 0.001
CRP (M ± SD)	33.8 ± 48.4	20.1 ± 24.5	53.9 ± 60.1	Z = −3.012, P = 0.003
Wuhan exposure (%)	26 (27.8)	18 (26.1)	8 (33.3)	χ^2 = 0.957, p = 0.328
Co morbidities (%)	50 (53.7)	29 (42.1)	21 (87.5)	χ^2 = 14.8, p < 0.01
Diabetes	21 (22.5)	8 (11.6)	13 (54.2)	χ^2 = 16.7, p < 0.01
Hypertension	23 (24.7)	7 (10.1)	16 (66.8)	χ^2 = 30.6, p < 0.01
hepatitis B	11 (11.8)	7 (10.1)	4 (16.7)	χ^2 = 0.628, p = 0.409
Heart disease	13 (13.9)	4 (5.8)	9 (37.5)	χ^2 = 14.9, p < 0.01
Renal dysfunction	10 (10.7)	2 (2.9)	8 (33.3)	χ^2 = 17.2, p < 0.01
Abnormal liver function	13 (13.9)	9 (13.0)	4 (16.7)	χ^2 = 0.194, p = 0.659
others	5 (5.4)	3 (4.3)	2 (8.3)	χ^2 = 0.556, p = 0.456

White blood count cell (WBC), neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (d-NLR) (neutrophil count divided by the result of white cell count minus neutrophil count), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR), C-reactive protein (CRP), lymphocyte (LYM), Neutrophils (NEU), Monocyte (MON).

predictors for the prognosis of patients with viral pneumonia. By collecting the data from 93 laboratory-confirmed cases, we attempted to determine the effect of sex, age, CRP, WBC count, NLR, LMR, PLR, and co morbidities on the length of stay of patients with COVID-19 pneumonia.

2. Materials and methods

2.1. Patients

We performed a retrospective study on the clinical characteristics of laboratory confirmed cases with COVID-19. Patients with complete clinical data, including 69 non-severe and 24 severe cases, were randomly selected. Cases were diagnosed on the basis of the interim guidance of the World Health Organization (WHO) [5] and diagnosis and treatment guidelines of COVID-19 in China [8]. Non-severe patients met all following conditions: (1) Epidemiology history, (2) Fever or other respiratory symptoms, (3) Typical CT image abnormities of viral pneumonia, and (4) Positive result of RT-PCR for SARS-CoV-2 RNA. Severe patients additionally met at least one of the following conditions: (1) Shortness of breath, RR ≥ 30 times/min, (2) Oxygen saturation (Resting state) ≤ 93%, (3) PaO_2/FiO_2 ≤ 300 mmHg. Patients with COVID-19 were confirmed by a positive result from the high-throughput sequencing or real-time reverse transcriptase-polymerase chain reaction assay for nasal and pharyngeal swab specimens [1]. Only the laboratory-confirmed cases were included in the analysis. The imperative of informed consent was waived in light of the anonymous, retrospective, and observational character of this study.

2.2. Clinical characteristics and laboratory data

Epidemiological characteristics, including recent exposure history, clinical symptoms and signs, and laboratory findings, were obtained from electronic medical records and telephone confirmation. Laboratory assessments consisted of complete blood count, blood chemistry and CRP. The severity of COVID-19 was defined on the basis of international guidelines for community-acquired pneumonia. First, the endpoint of non-severe time (NST) was the admission to the intensive care unit (ICU), cure and discharge, or mechanical ventilation. Second, severe time was defined as the time from observation of severe illness to the date of death, symptom reduction redefined as mild, or the end point time of follow-up until February 20, 2020. Given that clinical observations are still ongoing, a fixed time frame, that is, within 28 days, has not been applied to these endpoints.

2.3. Statistical analysis

Continuous variables were expressed as the appropriate means and standard deviations or medians and interquartile ranges. Categorical variables were summarized as the counts and percentages in each category. We grouped the patients into severe and non-severe COVID-19 according to the interim guidance of the World Health Organization (WHO) [5] and diagnosis and treatment guidelines of COVID-19 in China [5,8], which included the clinical management of severe acute respiratory infection in suspected cases. Wilcoxon rank sum tests were applied to continuous variables, and chi-square and Fisher's exact tests were used for categorical variables. The optimal cut-off values of the continuous NLR, d-NLR, PLR, and LMR were calculated by applying the receiver operating curve (ROC) analysis [15]. Hazard risk (HR) and 95% confidence interval (CI) were used as common measures to assess relative risk. Enter elimination binary logistic regression analysis was conducted to determine the influence of age, gender, and all other significant factors. P < 0.05 was recognized as statistically significant. All these statistical calculations were performed using the SPSS 17.0 software (SPSS Inc, Chicago, USA).

3. Results

3.1. Results of WBC count, NLR, LMR, PLR, CRP, d-NLR, and clinical characteristics in the study subjects

The demographics and clinical characteristics in the study subjects are shown in Table 1. The proportion of selected severe cases, including critical illness, was 25.8%. The average age was 58 years old, with 83 years old as the maximum. The average age of non-severe cases was 42 years old, with 7 months old as the minimum. The age, WBC count, NLR, LMR, PLR, CRP, and d-NLR of severe patients were significantly higher than those of non-severe patients. However, no significant difference was observed in terms of gender. All patients did not contact with wild animals. However, the ratio of patients, who recently traveled to Wuhan or contacted with people from Wuhan were documented in 27.8% (26/93) and 73.1% (68/93), respectively. Fever (83.8%) and

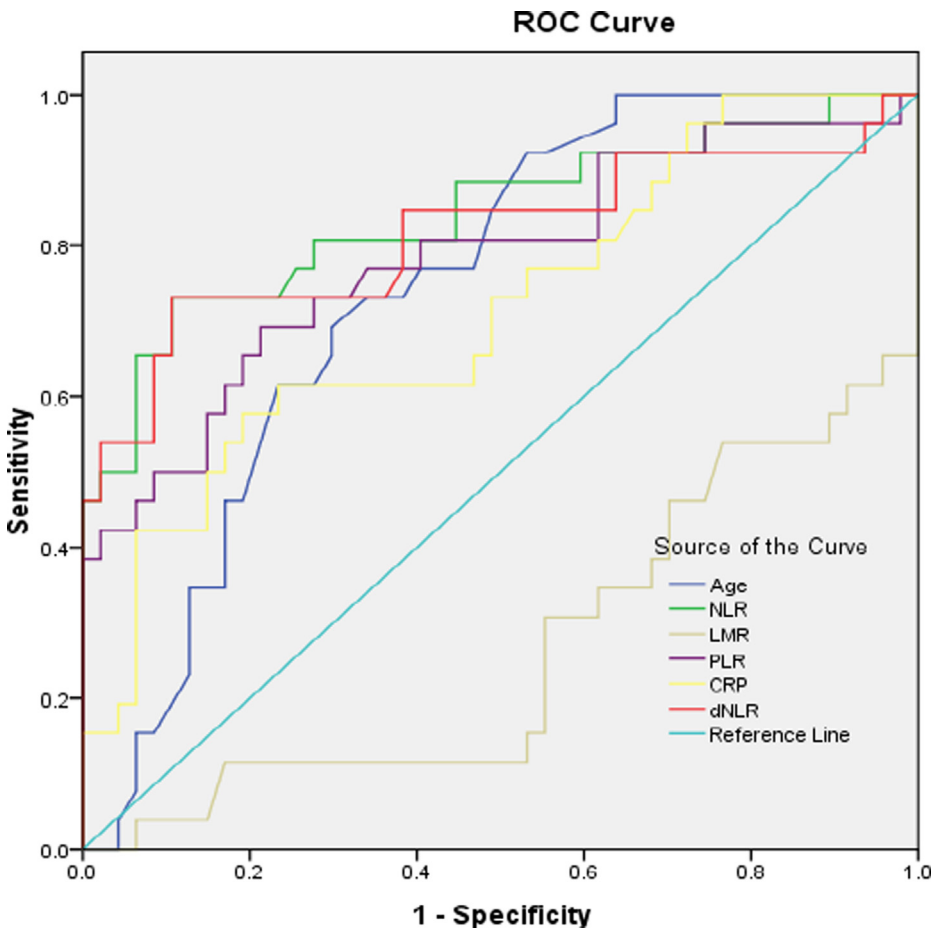

Fig. 1. ROC curve used to distinguish patients with severe and non-severe COVID-19.

cough (67.7%) were the first and most common symptoms before admission. Lymphopenia and neutrophilia were observed in 80.6% and 51.6% of patients, respectively. The laboratory reference values of LYM, NEU, and MON were 1.2–3.4, 1.8–6.3, and 0.1–0.6 E9/L, respectively. Most severe cases exhibited other co morbidities, followed by hypertension (66.8%), diabetes (54.2%), heart failure (37.5%), and renal insufficiency (33.3%). The severe case patients showed significantly high frequencies in the occurrence of diabetes ($p < 0.01$), hypertension ($p < 0.01$) and renal dysfunction ($p < 0.01$).

3.2. Use of the optimum cut-off values of laboratory results to discern severe from non-severe COVID-19 infection

Given that NLR, LMR, PLR, d-NLR, WBC count, and CRP were used to identify patients with severe or non-severe cases of COVID-19, patients with pneumonia were limited. No unified laboratory reference value was found. Therefore, we analyzed the optimal cut-off values calculated by the ROC analysis, and the ROC curves were presented in Fig. 1. In Fig. 1, areas under the curve (AUC) of age, NLR, d-NLR, CRP, LMR and PLR were 0.743, 0.841, 0.815, 0.714, 0.265, and 0.784. LMR could not be used as a potential diagnostic biomarker for subsequent analysis because its AUC was less than 0.50. The optimal cut-off values were 3.3, 2.8, and 180 for NLR, d-NLR, and PLR, respectively. The highest specificity and sensitivity were 0.636 and 0.88, 0.55 and 0.84, 0.44 and 0.77 for NLR, d-NLR, and PLR, respectively. The optimum cut-off values of age, WBC count, and CRP were 49.5 years, 7.2E9/L, and 20.3 mg/L, respectively (see Table 2).

Table 2
Areas under the curve (AUC) of age, NLR, d-NLR, PLR, CRP and LMR.

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Age	0.743	0.057	0.001	0.631	0.854
NLR	0.841	0.053	0.000	0.737	0.945
LMR	0.265	0.064	0.001	0.141	0.390
PLR	0.784	0.060	0.000	0.666	0.901
CRP	0.714	0.064	0.003	0.589	0.839
d-NLR	0.815	0.060	0.000	0.697	0.933

The test result variable(s): Age, NLR, LMR, PLR, CRP, d-NLR has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
[a] Under the nonparametric assumption.
[b] Null hypothesis: true area = 0.5.

3.3. Kaplan–Meier curves of NLR, d-NLR, and PLR for determining the factors that affect COVID-19 progression

To identify the factors that affect COVID-19 progression, eight potential factors were included in the analysis by using the Kaplan–Meier curve and the univariate Cox regression model. Furthermore, age, sex, and the significant factors in univariate analysis were included to determine their influences on non-severe time further. Figs. 2, 3 and 4 showed that the evaluated NLR, d-NLR, and PLR had slight or significantly unfavorable NST, respectively. Evaluated NLR (HR 2.46, 95% CI 1.98–4.569), d-NLR (HR 1.92, 95% CI 0.817–3.496), and PLR (HR

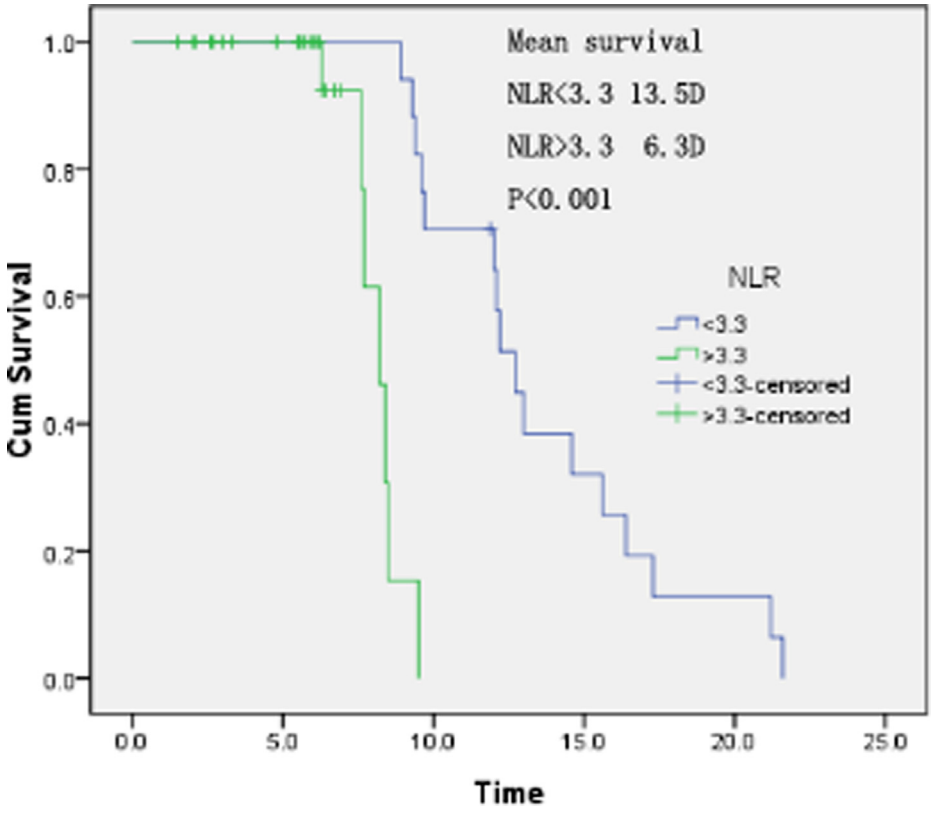

Fig. 2. Kaplan–Meier curves of NLR for non-sever of COVID-19.

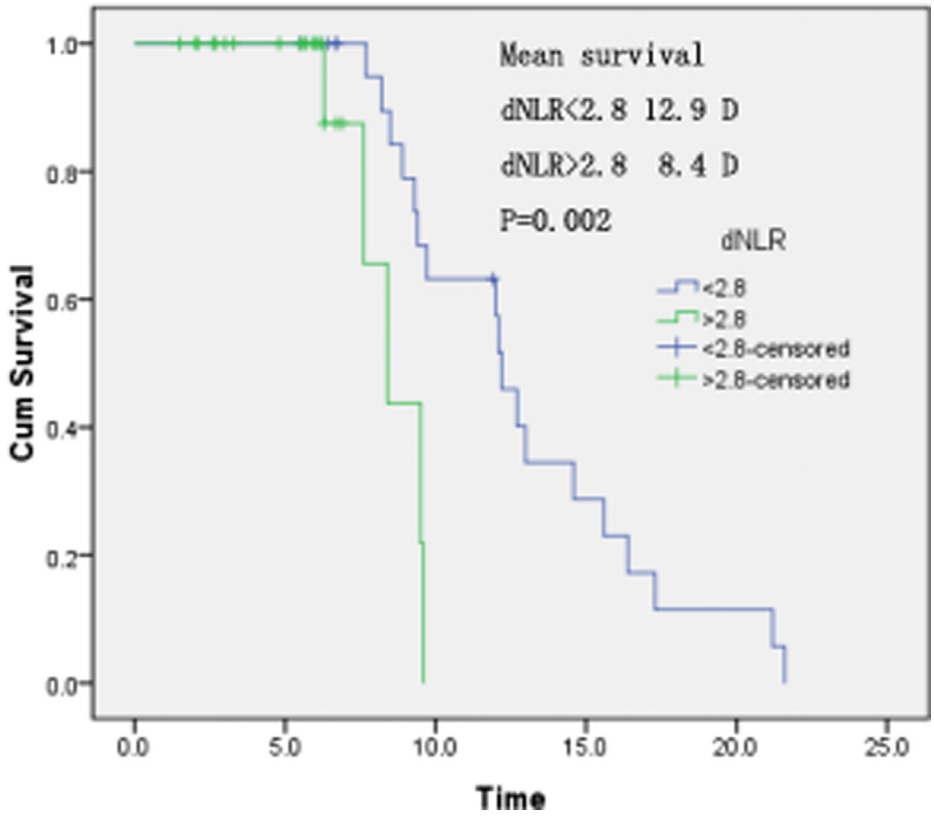

Fig. 3. Kaplan–Meier curves of d-NLR for non-sever of COVID-19.

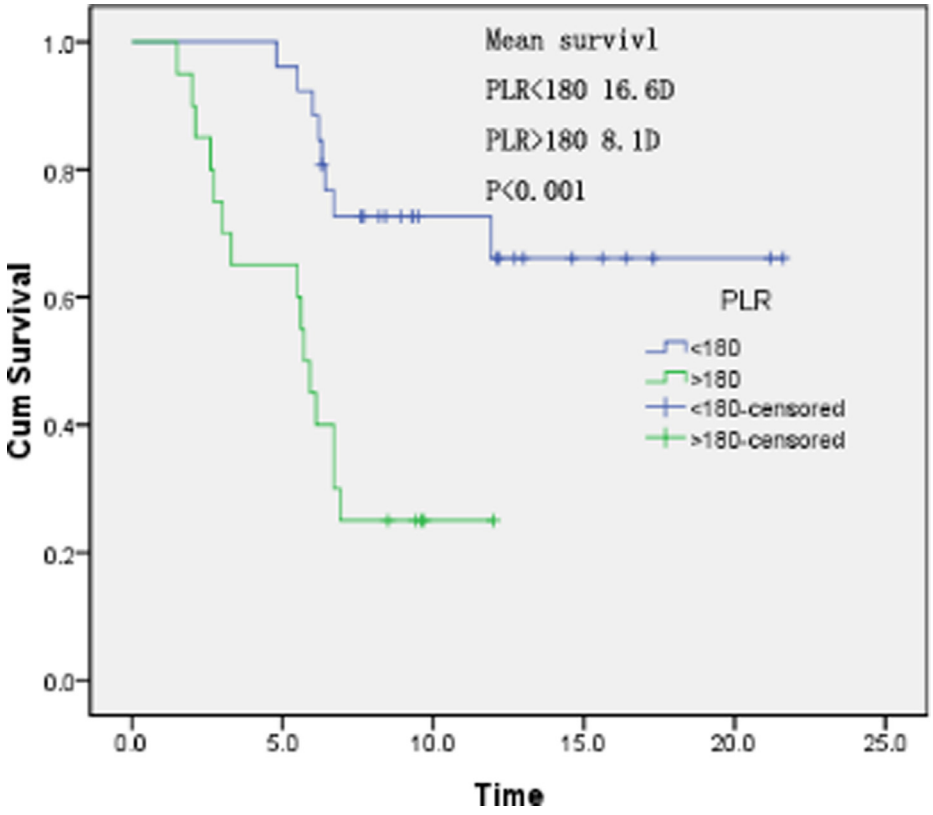

Fig. 4. Kaplan–Meier curves of PLR for non-sever of COVID-19.

1.023, 95% CI 0.921–1.756) identified by multivariate Cox regression were considered independent factors associated with COVID-19 progression. The category of non-severe COVID-19 patients, who met the both criteria including that age was greater than 49.5 years old and the NLR was greater than 3.3, should be closely attended because 46.1% of these patients would transform into severe cases with the mean time of 6.3 days. In contrast, the category of non-severe COVID-19 patients, who did not met the both criteria mentioned above, would discharged at approximately 13.5 days.

3.4. Association of NLR, d-NLR, and PLR results with the risk of COVID-19 pneumonia

To identify the factors that may affect COVID-19 progression, we obtained the crude odds ratio (OR) after conducting the logistic regression analysis (Table 3). Given that the blood test results were influenced by age and gender, we excluded the possible effects of age and gender and obtained the adjusted OR after the adjustment of gender and age. The results showed that NLR was positively correlated with the risk of COVID-19 (Table 3). Nevertheless, the risks of WBC, CRP, PLR, and d-NLR were unclear.

Table 3
The OR and ORa in each of the NLR, d-NLR, PLR.

Indicators	Crude odds ratio (OR)	*P*	Adjusted odds ratio (ORa)*	*P*
WBC	1.223 (0.891–1.756)	0.132	1.118 (0.888–1.543)	0.146
CRP	1.323 (0.961–2.086)	0.109	1.206 (0.898–2.045)	0.138
PLR	1.023 (0.921–1.756)	0.166	1.018 (0.988–1.749)	0.252
d-NLR	1.932 (0.817–3.496)	0.134	1.901 (0.841–4.300)	0.123
NLR	2.462 (1.981–4.569)	0.044	2.886 (2.064–4.860)	0.019

* Adjustment for age and gender.

4. Discussion

COVID-19 has elicits a rapid spread of outbreak with the human-to-human transmission, with a median incubation period of 3 days and a relatively low fatality rate [1]. At the end date of data collection (2020-02-18), more than 70,000 cases of COVID-19 were confirmed, and 1800 cases died. Mortality was less than 2.5% (CDC, China). In recent publications [1,8], the clinical characteristics of COVID-19 are similar to those of SARS-CoV. Fever and cough were the dominant symptoms, whereas gastrointestinal symptoms were rare, suggesting the difference in viral tropism compared with SARS-CoV, MERS-CoV, and influenza [11]. Fever occurred in only 43.8% of patients on initial presentation and developed in 83.4% after hospitalization. The absence of fever in COVID-19 was more frequent than in SARS-CoV (1%) and MERS-CoV infection (2%) [3,6], and such patients may be missed if the surveillance case definition focused heavily on fever detection [12]. Consistent with the two recent reports [13], lymphopenia is common and severe in some cases. Significantly high frequencies of severe cases were observed in elder patients with diabetes or hypertension (Table 1). The clinical characteristics of these patients are similar to those reported in previous studies [2,3,17].

After the discussion of the clinical features of COVID-19, we analyzed the immunological characteristics of peripheral blood in patients with COVID-19. In the present study, our results first proved our hypothesis and indicated that elevated NLR was an independent prognostic biomarker that affected pneumonia progression in COVID-19 patients. In addition, the integration of elevated neutrophil-to-lymphocyte ratio (NLR) to prognostic nomograms may lead to improved prediction. Our findings were consistent with those of previous studies on the relationship between NLR and prognosis of many other infectious diseases [14]. The following reasons may account for the findings. On the one hand, neutrophil (NEU) is a major component of the leukocyte population that activates and migrates from the venous system to the immune organ or system. NEU releases large amounts of

reactive oxygen species that can induce cell DNA damage and free the virus from the cells. Thus, antibody dependent cell mediated cell (ADCC) may kill the virus directly, expose virus antigen, and stimulate cell-specific and humoral immunities [15]. In addition, NEU interacts with distinct cell populations and produces numerous cytokines and effector molecules, such as circulating vascular endothelial growth factor (VEGF). VEGF stimulates tumor angiogenesis, growth, and metastasis [16]. Compared with normal tissues, VEGF-A and VEGF-C have significantly higher expressions in COVID-19 patients [17], and the reduced expression of VEGF and VEGFR contributes to markedly inhibited tissue and organ damage. Furthermore, NEU can be triggered by virus-related inflammatory factors, such as interleukin-6 and interleukin-8, tumor necrosis factor-alpha and granulocyte colony stimulating factor, and interferon-gamma factors, produced by lymphocyte and endothelial cells [18–21]. On the other hand, human immune response triggered by viral infection mainly relies on lymphocyte [22], whereas systematic inflammation significantly depresses cellular immunity, which significantly decreases CD4+ T lymphocytes and increases CD8+ suppressor T lymphocyte [23]. Thus, virus-triggered inflammation increased NLR. Elevated NLR promoted COVID-19 progression. The clinical symptoms were increasingly severe, and the progress from admission to ICU, cure and discharge, or mechanical ventilation was rapid.

In our study, the applicable thresholds for NLR, d-NLR, PLR, and LMR were observed using the ROC curve. The optimal threshold at 3.3 for NLR showed a superior prognostic possibility of clinical symptoms to change from mild to severe, which had the highest of sensitivity and specificity and the largest of AUC. When age $\geq$ 49.5 years old and NLR $\geq$ 3.3, 46.1% of the COVID-19 patients with mild disease will become severe, and the mean time is 6.3 days. So, these patients must be closely attended by clinicians. By contrast, when age $<$ 49.5 years old and NLR $<$ 3.3, COVID-19 patients with mild disease can be cured and discharged at approximately 13.5 days. The difference included numerous COVID-19 patients from a different geographic region and race may be an important factor that contribute to this phenomenon. NLR was a very useful indicator, and its clinical application was mainly seen in tumor-related diseases [24], autoimmune diseases [25], bacterial infectious pneumonia [26,27], and tuberculosis [28]. It could also be seen in other diseases, such as secondary pulmonary infectious diseases [29]. In addition, other scholars had shown that NLR was an early new marker of aiv-h7n9 infection in patients [30]. However, the application of NLR in other viral pneumonia was rarely reported. In our study, we found that NLR can be used as a prognostic factor for covid-19. Finally, the findings of this study indicated that elevated NLR was an independent prognostic biomarker for COVID-19 patients. NLR can increase evaluated capacity on COVID-19 patients for clinician. Therefore, the usable NLR and age are recommended as practical tools to assess prognosis and to evaluate the severity of clinical symptoms in COVID-19 patients.

Several notable limitations existed in this paper. First, the data were obtained from a single clinical research center and not from multiple clinical research centers. Second, the experimental data are limited. Furthermore, the conclusion of this study may differ from the conclusions of other scholars at home and abroad and must be improved in clinical cases further. Finally, due to time limitations, a small number of patients with the mild illness have no accurate clinical data. Thus, a certain deviation existed. To mitigate the potential bias, we acquired reference on the existing international guideline to define the severity of COVID-19 because of its global recognition.

In conclusion, The COVID-19 epidemic may spread rapidly by human-to-human. The clinical manifestations of this disease can vary even in patients with the same viral infection; the severity of the condition may be related to the number of immune cells. Disease severity is an independent predictor of poor outcome. Age and NLR may be related to the severity of the infection and may also indicate the outcome of the condition. The conclusions of this study support that elevated NLR is an independent prognostic biomarker for COVID-19 patients.

CRediT authorship contribution statement

Ai-Ping Yang: Methodology, Software, Writing - original draft. **Jian-ping Liu:** Data curation, Validation, Project administration. **Wen-qiang Tao:** Writing - review & editing. **Hui-ming Li:** Investigation, Methodology.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2020.106504.

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