

# Predictive Value of Neutrophil to Lymphocyte Ratio for Disease Deterioration and Serious Adverse Outcomes in Patients with COVID-19: A Prospective Cohort Study

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## Research article

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# Abstract

**Background:** Early identification of patients who are at high risk of poor clinical outcomes is of great important in saving lives for patients with the novel corona virus disease 2019 (COVID-19) in context of limited medical resources.

**Objective:** To evaluate value of the neutrophil to lymphocyte ratio (NLR), calculated at hospital admission and in isolation, for prediction of the subsequent presence of disease aggravation and serious clinical outcomes (e.g., shock, death).

**Methods:** We designed a prospective cohort study of 352 hospitalized patients with COVID-19 between January 9 and February 26, 2020 in Yichang city, Hubei province. Patients with a NLR equal to and higher than the cutoff value derived from the receiver operating characteristic curve method were classified as the exposure group. The primary outcome was disease deterioration, defined as promotion of clinical classifications of the disease during hospitalization (e.g., moderate to severe/critical; severe to critical,). The secondary outcomes were shock and death occurred during the treatment.

**Results:** During the follow up, 51 (14.5%) patients' condition deteriorated, 15 patients (4.3%) complicated septic shock, and 15 patients (4.3%) died. NLR was higher in patients with deterioration than those without (median: 5.33 vs. 2.14,  $P < 0.001$ ), as well as between patients with and without serious clinical outcomes (shock vs. no shock: 6.19 vs. 2.25,  $P < 0.001$ ; death vs. survival: 7.19 vs. 2.25,  $P < 0.001$ ). NLR measured at hospital admission had high value in predicting subsequent disease deterioration, shock and death (all the areas under the curve  $> 0.80$ ). The sensitivity of  $\geq 2.6937$  for the NLR in predicting subsequent disease deterioration, shock and death were 82.0% (95% confidence interval, 69.0 to 91.0), 93.3% (68.0 to 100), and 92.9% (66.0 to 100); and the corresponding negative predictive values were 95.7% (93.0 to 99.2), 99.5% (98.6 to 100) and 99.5% (98.6 to 100), respectively.

**Conclusions:** The NLR measured at admission and in isolation can be used to effectively predict subsequent presence of disease deterioration and serious clinical outcomes for patients with COVID-19.

## Background

The worldwide novel corona virus disease 2019 (COVID-19) pandemic has caused great loss of lives. According to the WHO COVID-19 dashboard, as of June 29, 2020, about 500 thousand were died out of a total of  $>10$  millions confirmed cases, with an average mortality of 4.99%. Mortality was positively correlated with severity of the disease. A summary of a report of 72314 cases in China indicated that case-fatality rate was as high as 49% in critical cases, while the average mortality in all confirmed cases was 2.3% [1]. Early identification of patients with COVID-19 who are at high risk of poor clinical outcomes is therefore of great important [2].

Neutrophil to lymphocyte ratio (NLR), whether in isolation or in combination with other risk factors, is identified as a useful marker in distinguishing severe cases from mild/moderate cases and is associated

with mortality of the disease [3-9]. However, little is known about predictive value of the NLR for aggravation of the disease (e.g., mild/moderate progress to severe/critical, severe deteriorate to critical) and serious clinical outcomes (e.g., shock, death). We conducted a prospective cohort study to evaluate value of using the NLR measured at hospital admission for prediction of the subsequent presence of poor clinical outcomes.

## Methods

### Study design and data collection

We conducted a prospective cohort study of COVID-19 patients who received medical treatment at the Third People's Hospital of Yichang, Hubei province from January 9 to February 26, 2020. All patients were confirmed by laboratory tests (positive for RT-PCR of nasal and pharyngeal swab specimens and/or specific IgM/G antibody assay of serum) before the admission and were followed up till the discharge or death in March 25, 2020. Basic information (e.g., age, gender, smoking, drinking, and history of co-morbidities) was collected through face to face interviews with the patients using a standardized questionnaire. Complete blood cell counts were conducted at hospital admission. Progression, treatment and clinical outcomes of the disease were recorded. The study was approved by the ethics committee of the First Affiliated Hospital of Fujian Medical University. The hospital was in charge of supporting the treatment of patients with COVID-19 in Yichang city.

### Exposure and outcome

Patients with a NLR, calculated by the neutrophil and lymphocyte data measured at hospital admission, equal to and higher than the cutoff value were categorized as the exposure group, otherwise were classified as the control group. The illness condition at hospital admission was evaluated and classified into mild/moderate, severe, and critical according to the diagnosis and treatment plan for COVID-19 (7<sup>th</sup> version) issued by the National Health Commission of the People's Republic of China [10]. Patients were reclassified if their condition worsen and reached a higher classification criterion.

The primary outcome was disease deterioration, defined as promotion of the disease classification types during hospitalization, including from mild/moderate to severe and/or critical, severe to critical. The secondary outcomes were shock and death occurred during the treatment.

### Data analysis

NLR was expressed as the medians (inter-quartile range) since the data is non-normal distribution ( $P < 0.001$  for Kolmogorov-Smirnov test). Categorical data were expressed as n (%) between patients with and without disease deterioration. Difference between the two groups was compared by chi-square or Fisher's exact test (if applicable) for categorical variables. Box diagram of the distribution of NLR between patients with and without the outcomes (i.e. disease deterioration, shock, death) were shown and compared by Mann-Whitney *U*-test.

Predictive performance of the NLR for disease deterioration, shock and death was assessed by estimating the area under the curve and the corresponding 95% confidence intervals (95% CI) of the receiver operating characteristic curve method. Cutoff value and the corresponding sensitivity, specificity, positive predictive value and negative predictive value were estimated.

The association of higher NLR (defined as the NLR of  $\geq$  the cutoff value) with the risk of disease deterioration, shock and death were further estimated by Cox proportional hazards model, in which potential confounders included maternal age ( $< 60$  or  $\geq 60$  years), gender (male or female), smoking (yes or no), drinking (yes or no), clinical type at admission (mild/moderate, severe, or critical) and history of chronic diseases (yes or no, defined as history of any one of hypertension, diabetes mellitus, coronary heart disease, cerebral vascular disease, chronic obstructive pulmonary disease and cancer). The Kaplan-Meier curve method was used to compare the cumulative risk of disease deterioration, shock and death between patients with  $\geq$  and  $<$  the cutoff value. All statistical tests were conducted using IBM SPSS Statistics version 22.0. A two-sided P value  $<0.01$  was considered statistically significant.

## Results

### Baseline characteristics

A total of 352 patients with COVID-19 were included for the analysis. The mean (SD) age of patients in the cohort was 52.1(18.1) years; 190 patients (54.0%) were men and 117 patients (33.2%) had history of at least one co-morbidity. At hospital admission, 301 patients (85.5%) were classified as mild/moderate, 48 (13.6%) were severe and 3 (0.9%) were identified as critical. During the follow up, 51 (14.5%) patients' condition deteriorated, 15 patients (4.3%) complicated septic shock, and 15 patients (4.3%) died (Table S1). Baseline characteristics except smoking and drinking were found unbalance for patients with and without deterioration (Table 1).

### Predictive performance

NLR measured at hospital admission was available for 341 patients, with a range from 0.11 to 85.5. NLR was higher in patients with deterioration than those without (median: 5.33 vs. 2.14,  $P <0.001$ ), as well as between patients with and without serious clinical outcomes (shock vs. no shock: 6.19 vs. 2.25,  $P <0.001$ ; death vs. survival: 7.19 vs. 2.25,  $P <0.001$ ) (Table 1, Figure1).

NLR measured at hospital admission had high value in predicting disease deterioration, shock and death, with areas under the curve of 0.801, 0.830, and 0.828, respectively, and a cutoff value of 2.6937 (Figure 2). The sensitivity of  $\geq 2.6937$  for the NLR in predicting subsequent presence of disease deterioration, shock and death were 82.0% (95% CI, 69.0 to 91.0), 93.3% (68.0 to 100), and 92.9% (66.0 to 100), respectively; and the corresponding negative predictive values were 95.7% (93.0 to 99.2), 99.5% (98.6 to 100) and 99.5% (98.6 to 100), respectively (Table 2).

Compared with patients who had a NLR of  $< 2.6937$ , adjusted hazard ratio for disease deterioration, shock and death were 4.1, 13.1 and 11.3, respectively among those with a NLR of  $\geq 2.6937$  (Table S2). Cumulative risk of the clinical outcome was significantly higher in patients with a NLR of  $\geq 2.6937$  than those of  $< 2.6937$  (all  $P < 0.001$ , Figure S1).

## Discussion

In this study, we validated a cutoff value of 2.6937 for the NLR, calculated at hospital admission, as a useful predictor of the subsequent presence of disease deterioration and the occurrence of serious clinical outcomes, such as shock and death. COVID-19 Patients with a NLR of  $< 2.6937$  had a possibility in ruling out disease deterioration (negative predictive value of 95.7%), as well as serious clinical outcomes (negative predictive value of 99.5%).

Early detection of patients whose condition is likely to worsen may aid in delivering proper care and optimizing use of limited resources [2]. NLR of the peripheral blood is related to the systemic inflammatory state and disease activity and shows its prognostic value in cardiovascular diseases, autoimmune diseases, malignant tumors and infectious diseases [11-14]. For patients with COVID-19, besides severe lung lesions, the prominent derangement of the lymph hematopoietic system was noted [15]. An elevated NLR may reflect the severity of the COVID-19 and the immune status of the patients.

Recently, some retrospective studies had identified the role of NLR in discriminating severe patients and predicting mortality of the COVID-19 patients [3-8]. The NLR was also included as a variable in a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19 [2]. The present study prospectively validates the findings of these previous studies through a large sample of 352 patients and extends the role of NLR in predicting disease deterioration and serious clinical outcomes, such as shock. Further, the present study identify a NLR cutoff value of 2.6937, by which most patients ( $\geq 82.0\%$ ) whose condition would worsen and serious clinical outcomes would occurred were included in the high risk group ( $NLR \geq 2.6937$ ) and the negative predictive value (the possibility of ruling out the outcomes) of a ratio below the cutoff value was  $\geq 95.7\%$ . The finding may improve the accuracy of clinical decisions made at hospital admission for clinicians in treating patients with COVID-19, especially in regions with high case volume and/or limited medical resources.

The present study has some limitations. First, the sample size was large but might not enough in evaluating the predictive performance of the NLR for shock and death since only 15 shocks and 14 deaths were included in the analysis in this cohort, resulted in a wide range of the 95% confidence interval for the sensitivity of shock and death. Second, mortality of the disease may affect the performance of NLR in predicting the outcomes. Studies on the applicability of the results in populations with various mortalities of the disease were warranted.

## Conclusion

In conclusion, in this prospective cohort study of 352 patients with COVID-19, NLR calculated at hospital admission had high value in predicting subsequent presence of disease deterioration and serious clinical outcomes and may be worth to be promoted to areas of COVID-19 epidemic.

## **Abbreviations**

Confidence interval CI

Corona virus disease 2019 COVID-19

Neutrophil to lymphocyte ratio NLR

## **Declarations**

### **Ethics approval and consent to participate**

The study was approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University and was conducted in accordance with Chinese law and the Guidelines of the National Human Biomedical Research Policies. Written informed consent was obtained from the patients or the guardians before the investigation. Administrative permissions of the data were acquired by the authors for research purposes.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

Data and materials were not available.

### **Competing interests**

The authors declare that they have no competing interests.

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### **Author contributions**

ZYZ and JNW were responsible for conception of the study, data analysis and interpretation of findings. ZYZ, GPC and JNW advised on design. ZYZ and GPC collected the data. JNW analysed the data and interpreted the findings. JNW and ZYZ drafted the manuscript. JNW and GPC reviewed and edited the final draft. All authors approved the final draft.

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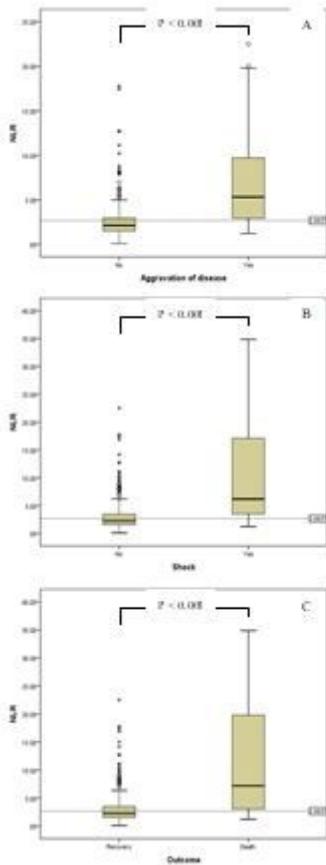
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## References

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020; 24.
2. Liang WH, Liang HR, Ou LM, et al. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. *JAMA Intern Med*. 2020; e202033.
3. Fu J, Kong J, Wang W, et al. The clinical implication of dynamic neutrophil to lymphocyte ratio and D-dimer in COVID-19: a retrospective study in Suzhou China. *Thromb Res*. 2020;192:3–8.
4. Wang CZ, Deng RR, Gou LY, et al. Preliminary study to identify severe from moderate cases of COVID-19 using combined hematology parameters. *Ann Transl Med*. 2020;8(9):593.
5. Shang WF, Dong JW, Ren YL, et al. The value of clinical parameters in predicting the severity of COVID-19. *J Med Virology*. 2020:1–5.
6. Yang AP, Liu JP, Tan WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. *Int Immunopharmacol*. 2020;84:106504.
7. Liu YW, Du XB, Chen J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. *J Infect*. 2020;81:e6–12.
8. Yan XS, Li F, Wang X, et al. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: a retrospective cross-sectional study. *J Med Virology*. 2020;1–9.
9. Tatum D, Taghavi S, Houghton A, et al. Neutrophil-to-lymphocyte ratio and outcomes in Louisiana Covid-19 patients. *Shock*. 2020; Jun 19.
10. National Health Commission of the People's Republic of China. Diagnosis and treatment plan of novel coronavirus pneumonia (The seventh version), 2020.
11. Huguet E, Maccallini G, Pardini P, et al. Reference values for neutrophil to lymphocyte ratio (NLR), a biomarker of cardiovascular risk, according to age and sex in a Latin American population. *Curr Probl Cardiol*. 2019; 100422.
12. Wang X, Qiu L, Li Z, Wang XY, Yi H. Understanding the Multifaceted Role of Neutrophils in Cancer and Autoimmune Diseases. *Front Immunol*. 2018;9:2456.
13. Mei Z, Shi B, Wang J, et al. Prognostic role of pretreatment blood neutrophil-to-lymphocyte ratio in advanced cancer survivors: a systematic review and meta-analysis of 66 cohort studies. *Cancer Treat Rev*. 2017;58:1–13.

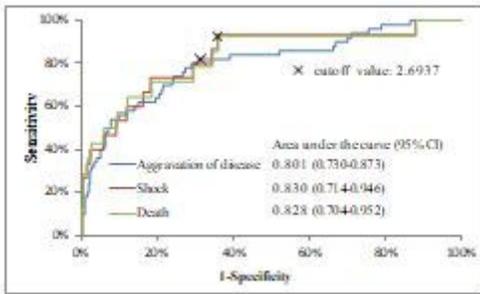
14. Russell CD, Parajuli A, Gale HJ, et al. The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: a systematic review and meta-analysis. *J Infect.* 2019;78(5):339–48.
15. Yao XH, Li TY, He ZC, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. *Zhonghua Bing Li Xue Za Zhi.* 2020;49(0):E9.

## Figures



**Figure 1**

Neutrophil to lymphocyte ratio for patients with and those without disease deterioration, shock and death. Disease deterioration (panel A), shock (panel B) and death (panel C). The bottom and top edges of each box represent the first (P25) and third quartiles (P75), respectively. The band within the box represents the median (P50), and the whiskers represent values that are 1.5 times of the inter-quartile range. The horizontal line represents the cutoff value of 2.6937 for the neutrophil to lymphocyte ratio. Two extreme outliers (>3 times of the inter-quartile range), including a case with a neutrophil to lymphocyte ratio of 85.52 in the groups without adverse outcome and of 54.36 in patients with adverse outcome, were not shown. NLR represents neutrophil to lymphocyte ratio.



**Figure 2**

Receiver operating characteristic curves of neutrophil to lymphocyte ratios in predicting serious clinical outcomes in patients with COVID-19. CI represents confidence interval.