Preplanned Studies

Diagnostic Value of Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio in Patients with Severe COVID-19 — 7 PLADs, China, January 21–February 10, 2020

Yan Ma[1,&]; Dongshan Zhu[2,3,&]; Nannan Shi[4,&]; Lei Zhang[5]; Guangkun Chen[5]; Youwen Ge[1]; Zelei Zhang[4]; Renbo Chen[4]; Sihong Liu[5]; Yipin Fan[1]; Huamin Zhang[6,#]; Yanping Wang[4,#]

Summary

What is already known about this topic?

Coronavirus disease 2019 (COVID-19) causes symptoms ranging from mild to severe. Indicators for identifying severe COVID-19 infection have not been well identified, especially for young patients.

What is added by this report?

Both neutrophil-lymphocyte ratio (NLR) [area under curve (AUC): 0.80; the odds ratios (OR) and 95% confidence intervals (95% CI): 1.30 (1.13–1.50)] and platelet-lymphocyte ratio (PLR) [AUC: 0.87; OR (95% CI): 1.05 (1.01–1.09)] were determined to be indicators for recognition of patients with severe COVID-19 in young patients less than age 40.

What are the implications for public health practice?

NLR and PLR are useful indicators for identifying patients with severe COVID-19, especially in young patients less than age 40.

Novel coronavirus pneumonia (coronavirus disease 2019, COVID-19) can infect anyone and causes symptoms ranging from mild to severe. Previous studies demonstrated that severe COVID-19 had more unfavourable treatment outcomes compared to non-severe COVID-19 (*1*–*2*). Early diagnosis and timely treatment were essential to cure severe COVID-19 patients and curb the spread of disease. Yet, rapid and convenient inflammatory markers for identifying severe COVID-19 infection have not been well studied, especially for young patients. Evidence has shown that the lymphocytes count (especially the CD4+ and CD8+ T cell counts) decreased as infection progressed (*3*). Neutrophils and platelets were found to be important mediators of inflammation. In severe COVID-19 cases, neutrophil counts were increased (*4*), and platelet accumulation was common (*5*). Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have been used to evaluate systemic inflammation in neoplastic and cardiovascular diseases (*6*–*7*). Using data from 452 confirmed COVID-19 cases, we examined whether NLR and PLR values on admission may help us identify severe patients upon admission.

To better understand the association between NLR, PLR, and severity of patients with COVID-19, we conducted a multi-center observational study in 41 hospitals from 7 provincial-level administrative divisions (PLADs) of China, i.e., Shanxi, Hebei, Heilongjiang, Shaanxi, Anhui, Guangxi, and Sichuan between January 21, 2020 and February 10, 2020 (Supplementary Table S1, available in http://weekly.chinacdc.cn). The implementation sites of the 7 PLADs were selected based on the geographical distribution (namely Eastern, Western, and Central regions of China), and 41 hospitals from the 7 PLADs were chosen based on their willingness to participate. All of these hospitals were designated hospitals for treating COVID-19 patients.

In our study, all COVID-19 patients enrolled were confirmed by a laboratory test; the patients were excluded if core data such as routine blood laboratory data was incomplete at admission. Medical records of these patients were collected. The study was approved by the National Administration of Traditional Chinese Medicine and Institutional Review Board at each participating hospital. Due to the urgency in treating COVID-19 patients, the requirement for written informed consent from study participants was replaced by verbal consent. All data were supplied and analyzed in an anonymous format, without access to personal identifying information.

This study has been registered by the Chinese Clinical Trial Registry (Registration Number: ChiCTR2100042177) and approved by the Ethics Committee of the Institute of Clinical Basic Medicine of Chinese Medicine, China Academy of Chinese Medical Sciences (NO: P20009/PJ09).

De-identified demographic data [sex, age, body mass

index (BMI), and comorbidity] and onset symptoms (fever, cough, dry cough, fatigue, shortness of breath, and diarrhea) were collected from patients' medical records. Results of complete blood count upon admission — including neutrophil count, platelet count, and lymphocyte count to calculate NLR and PLR — were collected.

Patients were divided into two groups of non-severe and severe based on their physician's clinical diagnosis after admission. Severe cases were defined as having any of the following: 1) respiratory distress; 2) pulse oxygen saturation ≤93%; or 3) arterial partial pressure of oxygen (PaO_2) / oxygen concentration ≤300 mmHg.

Multivariable logistic regression models were used to estimate the odds ratio (OR) and 95% confidence interval (95% CI) between NLR and PLR and patient's clinical severity of COVID-19. Receiver-operating characteristic (ROC) curves were used to assess the diagnostic value for identifying severe COVID-19 cases. In subgroup analyses, we stratified by sex and age (<40 years, 40–59 years, and ≥60 years).

A total of 452 patients were analyzed in our study between January 21, 2020 and February 10, 2020. The median age of patients was 45 years [interquartile range (IQR): 33.0, 57.0]; 50.9% of the participants were men; 33.8% had at least one comorbidity and the median BMI was 24.3 (IQR: 21.5, 26.4). Of 451 cases, 11.9% of severe and 4.0% of critical cases; 84.1% of non-severe cases including 41 mild cases and 339 moderate cases, respectively. The most common symptoms were cough (61.3%), fever (49.1%), and fatigue (37.6%), as seen in Table 1. The median (IQR, Q1–Q3) NLR and PLR in severe COVID-19 patients on admission were 5.4 (3.2–10.7) and 207 (160, 302), and in non-severe patients were 2.5 (1.7–3.8) and 149 (110–211), respectively.

Each one-unit (e.g., from 2 to 3) increase of NLR and each 10-unit increase of PLR was associated with 7% and 1% higher odds of being a severe patient, respectively (adjusted for age, sex, BMI, comorbidity, and onset symptoms, P<0.01). The odds ratios and 95% confidence intervals (OR, 95% CI) for being a severe patient in age groups of <40, 40–59, and ≥60 years were 1.30 (1.13–1.50), 1.04 (1.01–1.08), and 1.09 (0.99–1.20) for NLR, and 1.05 (1.01–1.09), 1.00 (1.00–1.01), and 1.01 (0.97–1.04) for PLR, respectively.

The area under curve (AUC) for predicting severe illness was 0.75 (95% CI: 0.69–0.82) for NLR and 0.67 (0.59–0.74) for PLR in all patients (Figure 1-A).

TABLE 1. Characteristics of the patients enrolled.

Characteristics	Patients (N=452)
Age (years)	
Median (IQR)	45.0 (33.0–57.0)
Distribution [n (%)]	
<40	166 (36.7)
40–59	192 (42.5)
≥60	94 (20.8)
Sex [n (%)]	
Male	230 (50.9)
Female	222 (49.1)
BMI (kg/m^2)	
Median (IQR)	24.3 (21.5–26.4)
Distribution [n/N (%)]	
<18.5	23/368 (6.3)
18.5–23.9	146/368 (39.7)
24–27.9	147/368 (39.9)
≥28	52 /368 (14.1)
Wuhan-related exposure [n (%)]	
Yes	134 (29.6)
Close history to COVID-19 cases [n (%)]	
Yes	285 (63.1)
Comorbidities [n (%)]	
Any	153 (33.8)
Hypertension	82 (18.1)
Diabetes	37 (8.2)
Cardiovascular disease	17 (3.8)
Stroke	13 (2.9)
Others	36 (23.6)
Clinical Classification [n (%)]	
Mild	41 (9.1)
Moderate	339 (75.0)
Severe	54 (11.9)
Critical	18 (4.0)
Signs and symptoms on admission [n (%)]	
Fever	170 (37.6)
Cough	277 (61.3)
Dry cough	156 (34.5)
Fatigue	170 (37.6)
Shortness of breath	63 (13.9)
Diarrhea	35 (7.7)

Note: Others of comorbidities included pulmonary tuberculosis, chronic bronchitis, emphysema, hepatitis, depression, etc.
Abbreviations: IQR=interquartile range; BMI=body mass index.

The AUCs in male and female were similar to that in all patients. After sub-analyses by age, the AUC in age groups of <40, 40-59, and ≥60 years were 0.80 (0.64–0.95), 0.75 (0.64–0.87), and 0.68 (0.56–0.80) for NLR, respectively, and 0.87 (0.78–0.86), 0.67 (0.56–0.79), and 0.54 (0.42–0.66) for PLR, respectively (Figure 1). The ideal cut-off values for predicting severe COVID-19 infection in patients less than age 40 for NLR and PLR were 3.1 and 192.

DISCUSSION

These findings indicate that both NLR and PLR were associated with clinical severity of COVID-19 infection. Higher NLR and PLR were useful predictors in diagnosis and early recognition of severe illness in younger patients of age <40 years. The benefits of using NLR and PLR measurements are because they are simple, rapid, and inexpensive, while also being associated with less patient discomfort, as only peripheral blood samples are required for testing. Furthermore, these values are easily evaluated in most hospital laboratories (*8*).

This study was subject to some limitations. Because we collected data from medical records, some demographic variables with missing values were not

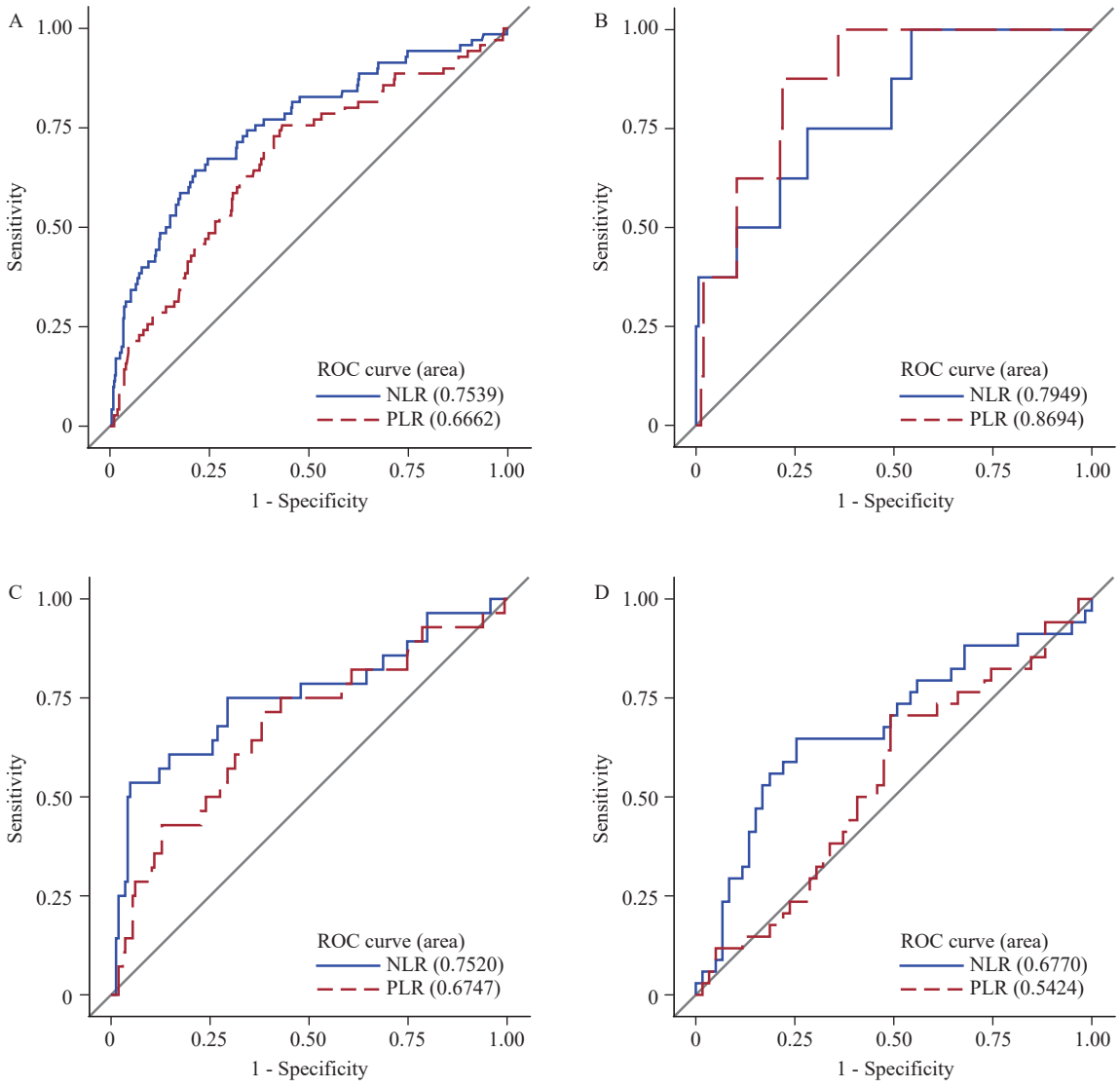

FIGURE 1. The area under curve for predicting severe COVID-19 infection for NLR and PLR in (A) all COVID-19 patients, (B) COVID-19 patients <40 years, (C) 40–59 year, and (D) ≥60 years.
Note: abbreviations: ROC=receiver operating characteristic; NLR=neutrophil-lymphocyte ratio; PLR=platelet-lymphocyte ratio. The blue curve represents the ROC of NLR and the red curve represents the ROC of PLR.

included, such as occupation, education level, and smoking status. This may cause some residual bias. Also, we only used the measurement of NLR and PLR upon admission. Thus, the trajectory of NLR and PLR and their association with clinical course could not be analyzed.

In conclusion, neutrophil, lymphocyte, and platelet counts are a part of routine blood tests, and NLR and PLR values can both be acquired in just five minutes. Because of this, NLR and PLR are recommended as indicators to identify severe COVID-19 patients, especially in young patients under 40 years old. This may help facilitate effective care and prioritize medical resources during a COVID-19 outbreak.

Conflicts of interest: No conflicts of interest reported.

Acknowledgments: All participants from 41 hospitals (Supplementary Table S1) in the study.

Funding: Supported by "CACMS Innovation Fund (CI2021A00704), COVID-19 Project of National Administration of Traditional Chinese Medicine (2020ZYLCYJ07-1), COVID-19 project of National Administration of Traditional Chinese Medicine (GZY-KJS-2021-007), the Fundamental Research Funds for the Central public welfare research institutes (Z-0696)".

doi: 10.46234/ccdcw2022.047

[#] Corresponding authors: Huamin Zhang, zhanghm@mail.cintcm.ac.cn; Yanping Wang, wangyanping4816@163.com.

[1] Department of Infectious Disease Prevention, Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing, China; [2] Department of Epidemiology, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, Shandong Province, China; [3] Centre for Health Management and Policy Research, School of Public Health, Cheeloo College of Medicine, Shandong University [NHC Key Lab of Health Economics and Policy Research (Shandong University)], Jinan, 250012，China; [4] Chinese Medicine Standardization Research Center, Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing, China; [5] Institute of Information on Traditional Chinese Medicine, China Academy of Chinese Medical Sciences, Beijing, China; [6] Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing, China.

[&] Joint first authors.

Submitted: April 28, 2021; Accepted: January 18, 2022

REFERENCES

1. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) — China, 2020. China CDC Wkly 2020;2(8):113 – 22. http://dx.doi.org/10.46234/ccdcw2020.032.
2. Ma Y, Zhu DS, Chen RB, Shi NN, Liu SH, Fan YP, et al. Association of overlapped and un-overlapped comorbidities with COVID-19 severity and treatment outcomes: a retrospective cohort study from nine provinces in China. Biomed Environ Sci 2020;33(12):893 – 905. http://dx.doi.org/10.3967/bes2020.123.
3. Zhang XN, Tan Y, Ling Y, Lu G, Liu F, Yi ZG, et al. Viral and host factors related to the clinical outcome of COVID-19. Nature 2020;583(7816):437 – 40. http://dx.doi.org/10.1038/s41586-020-2355-0.
4. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, Borczuk A, Cools-Lartigue J, Crawford JM, et al. Targeting potential drivers of COVID-19: neutrophil extracellular traps. J Exp Med 2020;217(6):e20200652. http://dx.doi.org/10.1084/jem.20200652.
5. Zhang Y, Xiao M, Zhang SL, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020;382(17):e38. http://dx.doi.org/10.1056/NEJMc2007575.
6. Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W, et al. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. Lung Cancer 2017;111:176 – 81. http://dx.doi.org/10.1016/j.lungcan.2017.07.024.
7. Kurtul A, Ornek E. Platelet to lymphocyte ratio in cardiovascular diseases: a systematic review. Angiology 2019;70(9):802 – 18. http://dx.doi.org/10.1177/0003319719845186.
8. Balta S, Ozturk C. The platelet-lymphocyte ratio: a simple, inexpensive and rapid prognostic marker for cardiovascular events. Platelets 2015;26(7):680 – 1. http://dx.doi.org/10.3109/09537104.2014.979340.

SUPPLEMENTARY TABLE S1. List of 41 hospitals in the multi-center observational study.

Number	PLADs	List of hospitals
1	Shaanxi	Shangluo Central Hospital
2	Heilongjiang	The People's Hospital of QiTaiHe
3	Shaanxi	Xianyang Central Hospital
4	Anhui	The First Affiliated Hospital of Anhui University of Traditional Chinese Medicine
5	Hebei	Langfang Hospital of Chinese Medicine
6	Hebei	Xingtai Hospital of Chinese Medicine
7	Guangxi	The People's Hospital of GuangXi Zhuang Autonomous Region
8	Guangxi	The First People's Hospital of Fangchenggang
9	Sichuan	Mianyang Hospital of Traditional Chinese Medicine
10	Guangxi	Liuzhou People's Hospital
11	Sichuan	Affiliated Hospital of North Sichuan Medical College
12	Sichuan	The Public Health Clinical Center of Chengdu
13	Hebei	Shijiazhuang Fifth Hospital
14	Shanxi	The Fourth People's Hospital of Taiyuan
15	Sichuan	The First Hospital of Suihua City
16	Shaanxi	Ankang Hospital of Traditional Chinese Medicine
17	Guangxi	Beihai Hospital of Chinese Medicine
18	Heilongjiang	Harbin Infectious Disease Hospital
19	Hebei	Chengde Hospital of Traditional Chinese Medicine
20	Shanxi	Datong Fourth Hospital
21	Sichuan	Suining Central Hospital
22	Shanxi	Jinzhong Infectious Disease Hospital
23	Shanxi	Jincheng People's Hospital, Jincheng
24	Shaanxi	Hanzhong Central Hospital, Hanzhong,
25	Shanxi	Shuozhou People's Hospital, Shuozhou
26	Heilongjiang	Mudanjiang Kangan Hospital, Mudanjiang
27	Shanxi	Xinzhou People's Hospital,
28	Shanxi	Daqing Second Hospital
29	Heilongjiang	Jiamusi Infectious Disease Hospital
30	Shaanxi	Hanzhong Hospital for Infectious Diseases
31	Shaanxi	Shaanxi Infectious Disease Hospital
32	Shaanxi	Baoji Central Hospital
33	Shaanxi	Xi'an Chest Hospital
34	Heilongjiang	Qiqihar Institute for The Prevention and Treatment of Infectious Diseases
35	Shanxi	Fenyang Hospital of Shanxi Province
36	Heilongjiang	Shuangyashan People's Hospital
37	Heilongjiang	The Greater Khingan Range People's Hospital
38	Guangxi	The Fourth People's Hospital of Nanning
39	Shanxi	The Third People's Hospital of Linfen
40	Hebei	Hengshui Hospital of Chinese Medicine
41	Heilongjiang	The First Hospital of Qiqiha

Abbreviation: PLADs=provincial-level administrative divisions.