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

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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 (PaO₂) / 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 1A).

### TABLE 1. Characteristics of the patients enrolled.

| Characteristics | Patients (N=452) |
|-----------------|-----------------|
| Age (years)     | Median (IQR)    |
|                 | 45.0 (33.0–57.0)|
| Distribution [n (%)] | 166 (36.7)  |
| <40             | 192 (42.5)      |
| ≥60             | 94 (20.8)       |
| Sex [n (%)]     |                 |
| Male            | 230 (50.9)      |
| Female          | 222 (49.1)      |
| BMI (kg/m²)     | 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 (%)] | 134 (29.6) |
| Yes             | 285 (63.1)      |
| Close history to COVID-19 cases [n (%)] |                 |
| Yes             | 153 (33.8)      |
| Comorbidities [n (%)] |                 |
| Any             | 82 (18.1)       |
| Hypertension    | 37 (8.2)        |
| Diabetes        | 17 (3.8)        |
| Cardiovascular disease | 13 (2.9)   |
| Stroke          | 36 (23.6)       |
| Others          | 18 (4.0)        |
| 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 pulmonar 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.

This study was subject to some limitations. Because we collected data from medical records, some demographic variables with missing values were not...
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 (2020ZYLYC07-1), 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/ccdcw2020.047

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doi: 10.46234/ccdcw2022.047

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

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| Number | PLADs   | List of hospitals                                                                 |
|--------|---------|-----------------------------------------------------------------------------------|
| 1      | Shaanxi | Shaanluo 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 | Beihaip 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  | Jinhong 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.