Received: 27 February 2020 | Accepted: 12 March 2020

DOI: 10.1002/jmv.25767

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19

Rong Qu[1] | Yun Ling[1] | Yi-hui-zhi Zhang[2] | Li-ya Wei[2] | Xiao Chen[2] | Xu-mian Li[2] | Xuan-yong Liu[2] | Han-mian Liu[1] | Zhi Guo[2,5] | Hua Ren[3,4] | Qiang Wang[5]

[1]Department of Critical Care Medicine, Huizhou Municipal Central Hospital, Huizhou, China

[2]Department of Hematology and Oncology, National Cancer Center/National Clinical Research Cancer for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China

[3]Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[4]Department of Medical, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China

[5]Institute of Infection, Immunology and Tumor Microenvironment, Medical College, Wuhan University of Science and Technology, Wuhan, China

Correspondence

Zhi Guo, Department of Hematology and Oncology, National Cancer Center/National Clinical Research Cancer for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 518116 Shenzhen, China.
Email: guozhi77@126.com

Hua Ren, Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 100021 Beijing, China.
Email: renhua2009@hotmail.com

Qiang Wang, Institute of Infection, Immunology and Tumor Microenvironment, Medical College, Wuhan University of Science and Technology, 430065 Wuhan, China.
Email: wangqiang@wust.edu.cn

Abstract

Since December 2019, novel coronavirus infected pneumonia emerged in Wuhan city and rapidly spread throughout China. In severe novel coronavirus pneumonia cases, the number of platelets, their dynamic changes during the treatment, platelet-to-lymphocyte ratio (PLR) were a concern. We sought to describe the platelet feature of these cases. Single-center case series of the 30 hospitalized patients with confirmed coronavirus disease (COVID)-19 in Huizhou municipal central hospital from January 2020 to February 2020 were retrospectively analyzed. Demographic, clinical, blood routine results, other laboratory results, and treatment data were collected and analyzed. Outcomes of severe patients and nonsevere patients were compared. Univariate analysis showed that: age, platelet peaks, and PLR at peak platelet were the influencing factors in severe patients, multivariate analysis showed that the PLR value at peak platelet during treatment was an independent influencing factor in severe patients. The average hospitalization day of patients with platelet peaks during treatment was longer than those without platelet peaks ($P < .05$). The average age of patients with platelet peaks during treatment was older than those without platelet peaks ($P < .05$). The patients with significantly elevated platelets during treatment had longer average hospitalization days. And the higher PLR of patients during treatment had longer average hospitalization days. Single-center case series of the 30 hospitalized patients with confirmed COVID-19 in Huizhou Municipal Central Hospital, presumed that the number of platelets and their dynamic changes during the treatment may have a suggestion on the severity and prognosis of the disease. The patient with markedly elevated platelets and longer average hospitalization days may be related to the cytokine storm. The PLR

Rong Qu, Yun Ling, and Yi-hui-zhi Zhang are the co-first authors.

of patients means the degree of cytokine storm, which might provide a new indicator in the monitoring in patients with COVID-19.

KEYWORDS
coronavirus disease, cytokine storm, platelet value, platelet-to-lymphocyte ratio, risk factor

1 | INTRODUCTION

In December 2019, pneumonia cases of unknown origins, known as novel coronavirus pneumonia (NCP), occurred in Wuhan, Hubei province, China. The World Health Organization has recently officially named NCP as coronavirus disease in 2019 (COVID-19).[1] In the following month, the disease spread rapidly from Wuhan to other cities. So far, more than 70 000 COVID-19 cases have been confirmed in China. Internationally, cases have been reported in 24 countries and 5 continents. Patients' clinical manifestations mainly included fever, fatigue, nonproductive cough, and dyspnea. Patients' laboratory examinations included normal or reduced leukocyte count, reduced lymphocyte count, thrombocytopenia, elevated transaminase, elevated lactate dehydrogenase (LDH), elevated creatine kinase, and elevated myoglobin. Reduced lymphocyte count can occur in some severe cases.[2] At present, there is no effective therapy for COVID-19. Therefore, the group of diseases and the assessment of prognosis become more and more important.[3] The severity of diseases was according to the COVID-19 diagnosis and treatment scheme issued by the National Health Committee. Patients were divided into four groups, including light groups, medium groups, severe groups, and critically ill groups.

However, platelet-to-lymphocyte ratio (PLR) of COVID-19 between severe and nonsevere cases were not fully reported, which may have prognostic values and be important therapeutic targets. In this study, the number of platelets, their dynamic changes during the treatment, PLR of 30 laboratory-confirmed cases admitted to Huizhou Municipal Central Hospital was showed, the difference between severe and nonsevere cases was investigated.

2 | METHODS

Thirty patients with confirmed COVID-19 admitted to Huizhou Municipal Central Hospital from January 2020 to February 2020 were enrolled. This study was approved by the Ethics Committee of Huizhou Municipal Central Hospital (Huizhou, China). The diagnosis of COVID-19 was according to National Health Committee guidance and confirmed by RNA detection of the 2019-nCoV in the Chinese Center for Disease Prevention and Control. Only the laboratory-confirmed cases were included in the analysis. All the patients were at least 18 years of age. Patients with chronic lung diseases, hematological diseases, liver disease, having undergone radiotherapy and chemotherapy were excluded. The composite endpoint of the study was 21 February 2019. Finally, 30 discharged patients met the above criteria and were included in this study.

According to the COVID-19 diagnosis and treatment scheme issued by the National Health Committee, signs, symptoms, and comorbidities, patients were divided into severe cases and nonsevere cases. Clinical condition assessment criteria: according to the COVID-19 diagnosis and treatment plan issued by the National Health Committee of China, clinical classification is performed, which is divided into four types: light, ordinary, heavy, and critical. Mild: mild clinical symptoms, no pneumonia on imaging; common: fever, respiratory tract symptoms, and pneumonia on imaging; severe: meet any of the following: (a) shortness of breath, RR > 30 times/min; (b) resting state, means oxygen saturation ≤ 93%; (c) partial pressure of arterial oxygen (PaO2)/oxygen concentration (FiO2) ≤ 30 mm Hg (1 mm Hg= 0.133 kPa), pulmonary imaging shows that the lesions have progressed significantly within 50 to 48 hours, and those who are more than 50% are managed as heavy; critical: meet any of the following: (a) have respiratory failure and require mechanical ventilation; (b) have body weight; (c) combined with other organ failure requires ICU monitoring and treatment.

According to COVID-19 guidance by the National Health Committee, patients receive effective oxygen therapies including a nasal catheter, mask oxygen and high-flow oxygen therapy on the whole. Lopinavir was available. Treatment measures of severe cases and critically ill cases were different from nonsevere cases. On the basis of symptomatic treatment, preventing complications, preventing secondary infections, respiratory support, circulatory support was necessary. Symptomatic treatment was given in cases of reduced lymphocyte count and thrombocytopenia.

The information recorded included demographic data, medical history, symptoms, signs, laboratory findings, chest computed tomographic scans, and treatment measures. The samples for peripheral blood were collected on admission and during the hospital stay. Lymphocytes, platelets, alanine aminotransferase, aspartate aminotransferase, and LDH were detected in the clinical laboratory of Huizhou Municipal Central Hospital. On the basis of the patients' blood routine, PLR was calculated. Multivariate analysis of independent risk factors and relationship between PLR and prognosis.

Data are presented as mean and standard deviation unless stated otherwise. The nonparametric two-tailed Student *t* test was used to analyze variables. Differences in values between tested groups were regarded as significant at a value of $P \leq .05$. Correlation analysis used simple linear correlation, multifactor logistic regression analysis. Data were analyzed using SPSS 25. The optimal cut-off value, sensitivity (sensitivity), and specificity (specificity) of PLR were determined by analysis of receiver operating characteristic (ROC) curve. The statistical graphs were drawn using GraphPad Prism 6 software.

TABLE 1 The relationship of various indicators between nonsevere patients and severe patients

Index	Nonsevere patients	Severe patients	Statistics	*P* value
Age	49.44 ± 14.86	60 ± 5.29	2.52 (*t*)	.041
Time of hospitalization (mean ± standard deviation), d	15.33 ± 4.32	27 ± 1.41	3.745 (*t*)	.01
Platelet value at admission (mean ± standard deviation), $\times 10^9$/L	192.26 ± 58.12	169.67 ± 48.95	−0.645 (*t*)	.524
Lymphocyte value at admission (mean ± standard deviation), $\times 10^9$/L	1.01 ± 0.45	1.16 ± 0.55	0.54 (*t*)	.593
PLR at admission (mean ± standard deviation)	242.75 ± 173.74	160.02 ± 51.99	30.00 (χ^2)	.414
Peak of platelet during treatment (mean ± standard deviation), $\times 10^9$/L	301.22 ± 80.18	392 ± 123.38	1.776 (*t*)	.047
PLR at peak of platelet (mean ± standard deviation)	262.35 ± 97.78	626.27 ± 523.64	3.544 (*t*)	.001
ALT value at admission (mean ± standard deviation), U/L	33.59 ± 24.54	36 ± 19.52	0.163 (*t*)	.871
AST value at admission (mean ± standard deviation), U/L	43.56 ± 21.03	45.33 ± 12.90	0.143 (*t*)	.888
LDH value at admission (mean ± standard deviation), U/L	528.15 ± 188.64	772.33 ± 292.13	2.028 (*t*)	.052
Hormone use (number), %	18 (66.7%)	3 (100%)	−1.183 (*t*)	.247

3 | RESULTS

3.1 | Demographic characteristics

There were a total of 30 patients admitted with a median age of 50.5 years (36-65 years), including 16 males and 14 females. There were 27 cases in the nonsevere group and 3 cases in the severe group. Patients in the severe group are older.

3.2 | Correlation analysis between nonsevere patients and severe patients

The correlation between two groups in terms of age, length of hospitalization, the absolute value of lymphocytes, platelets, and so on are shown in Table 1 and Figures 1 and 2. Table 1 shows the difference between nonsevere group and severe group in the average age (49.44 vs 60 years) and the average length of hospitalization (15.33 vs 27 days), the statistics of two groups was statistical significance ($P < .05$). We also analyze some other indicators between the two groups, such as platelet value, absolute lymphocyte values, PLR, ALT, and AST, LDH at admission. But there are no significance between them. Unexpectedly, comparing the peak of platelet, it was found that the average platelet peak during the treatment of severe patients was 392×10^9/L, which was significantly higher than the nonsevere patients at 301×10^9/L. The PLR was 626, which was significantly higher than the PLR of nonsevere patients, which was 262. The date of the two groups was statistically significant ($P < .05$). In terms of hormone use, a total of 18 nonsevere patients used hormones during treatment, accounting for 66.7% of nonsevere patients, and 3 of the severe patients had used hormones, accounting for 100%, but these two groups of data have no statistical significance. Multivariate logistic

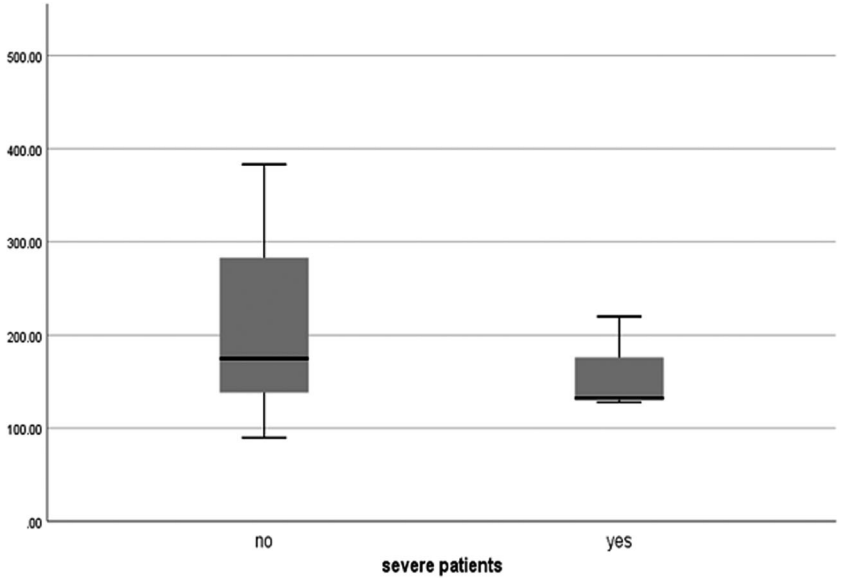

FIGURE 1 Platelet-to-lymphocyte ratio (PLR) at the admission of nonsevere patients and severe patients

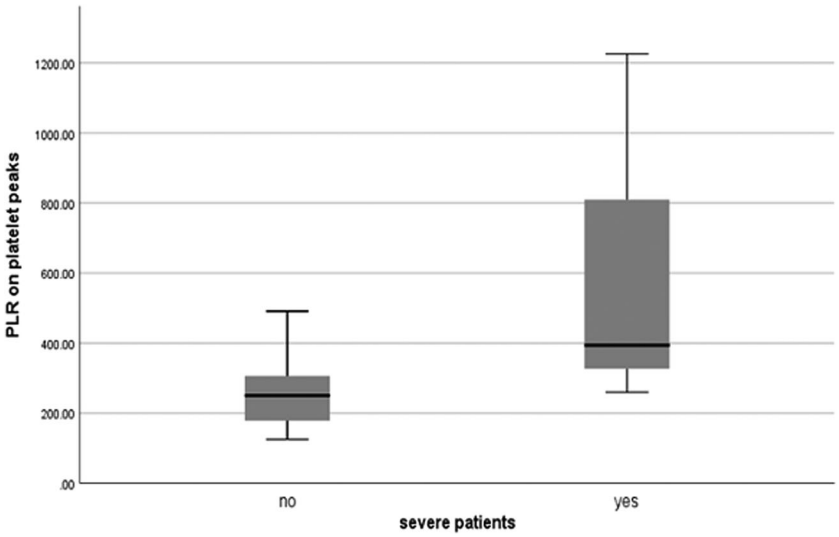

FIGURE 2 Platelet-to-lymphocyte ratio (PLR) at the peak of platelets in nonsevere patients and severe patients

regression analysis of age, platelet peak, and PLR at platelet peak during treatment showed that PLR at platelet peak during treatment was an independent influencing factor for critically ill patients. The results are shown in Table 2.

3.3 | Correlation between platelet trend and course of disease during treatment

Figure 3 shows the trend of platelet in three severe patients. We found the same trend in three nonsevere patients. And their platelet value was above 300×10^9/L. The platelet peak of group A was above 300×10^9/L during the treatment. The platelet peak of group B was under 300×10^9/L during the treatment. As shown in Table 3, patients in group A was older than patients in group B. Patients in group A had longer average hospitalization day. The difference between the two groups is statistically significant ($P < .05$).

3.4 | Correlation between platelet-to-lymphocyte ratio difference and disease course

Comparing the correlation between the difference (ΔPLR) the PLR at the time of admission and the maximum of PLR during treatment, and the length of hospitalization day. The data are shown in Table 4. The average ΔPLR in severe patients was 466.24 ± 471.86, while in nonsevere patients was 19.61 ± 130.40. By comparison, we found that the patients' ΔPLR was correlated with the length of hospitalization day. If ΔPLR increased more during treatment, the patient had longer hospitalization day and a greater possibility of severe pneumonia. On the contrary, if ΔPLR increased less during treatment, the patient had shorter hospitalization day endless possibility of severe pneumonia, as shown in Figure 4. By drawing the ROC curve, we can know that the cut-off value of ΔPLR is 126.7, the sensitivity is 100%, the specificity is 81.5% ($P = .014$). In clinical treatment, when the PLR value is greater than 126.7, we should raise our vigilance, patients may appear to increase the length of hospital stay and worsen the condition.

TABLE 2 Logistic regression analysis of risk factors in severe patients

	OR	95%CI
PLR2	0.993	0.983-1.003

Abbreviations: CI, confidence interval; OR, odds ratio.

4 | DISCUSSION

COVID-19 is an acute infectious disease caused by a new coronavirus (SARS-CoV-2), the first symptom of most patients is fever, and some patients may not have a fever in the early stage, only chills, respiratory symptoms, mild dry cough, fatigue, poor breathing, and diarrhea. Patients may gradually develop dyspnea. In severe cases, the disease progresses rapidly. MODS, septic shock, difficult to correct metabolic acidosis, and coagulation dysfunction may occur within a few days. Some patients have severe inflammatory storms leading to death.[4] Therefore, judging the development trend and prognosis of the disease at an early stage, and taking active and effective treatment for patients who may develop into severe illness can effectively reduce the mortality rate.

There are so many similarities between the outbreak of COVID-19 originated from Wuhan and SARS in Guangdong province in 2003. For example, they both occurred in winter and originated from the contact between live animals in the human-animal trading market and caused by an unknown coronavirus. Compared with SARS, they both are caused by human coronavirus infection. Although there are significant differences between 2019-nCOV and SARS-CoV in genetic characteristics, there are still many similarities in physical and chemical characteristics.[5-8] A retrospective analysis of SARS patients

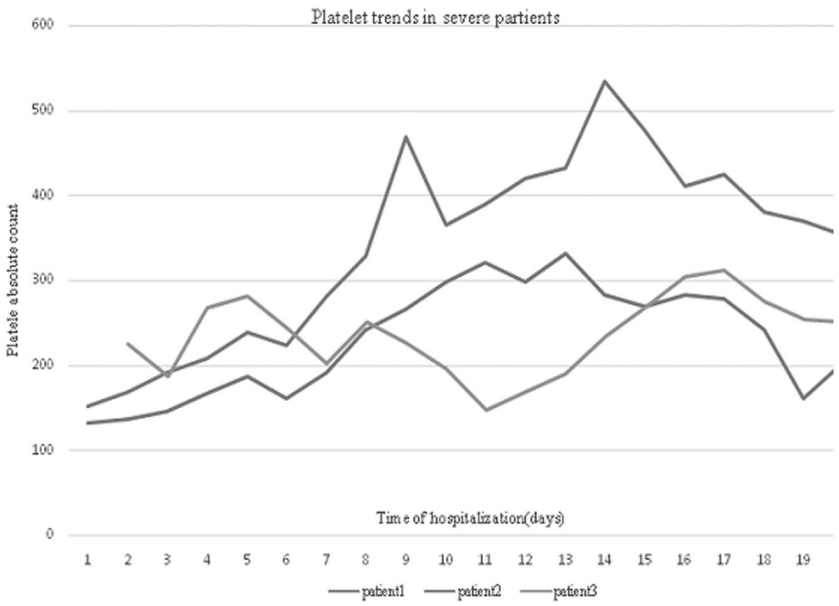

FIGURE 3 Platelet trends during treatment of severe patients

showed that 68% to 90% of diagnosed patients had peripheral lymphocytopenia, 20% to 45% had thrombocytopenia, and 20% to 34% had leukopenia.[9] Platelets are important immune cells in the human body, which play an important role in hemostasis, coagulation, vascular integrity maintenance, angiogenesis, innate immunity, inflammatory response, tumor biology and so on. Changes in its number and activity are closely related to a variety of diseases.[10,11] Platelets are produced by mature megakaryocytes in the bone marrow, and current studies have shown that a variety of cytokines, including TPO, IL-3, IL-6, IL-9, IL-11, and stem cell factor (SCF), can promote the production of megakaryocytes. In vitro experiments, the addition of mixed cytokines can stimulate the generation of megakaryocytes. SCF plays an important role in promoting the proliferation of megakaryocytes at the early stage of differentiation, while IL-3 and TP0 play a synergistic role in the differentiation of megakaryocytes. In state of inflammation, IL-6 can promote the generation of megakaryocytes by stimulating the increase of TPO level.[12-15] The absolute value of lymphocytes and platelet levels can be used as sensitive indicators to reflect the body's infection and inflammation control. But can these indicators have the same clinical value for COVID-19?

Therefore, we analyzed the changes in peripheral blood of the COVID-19 patients in 2019, and the association between the changes and the survival and prognosis of the patients. According to a report by Zhongnan Hospital affiliated to Wuhan University,[16] the total number of white blood cells in the peripheral blood of these patients in the early stage of the disease was normal or decreased, while the lymphocyte count was decreased. Liver damage and elevated inflammatory markers can occur in some patients. Our results show that the lymphocyte level at admission is related to the prognosis. The older patients with a lower count of lymphocyte and platelet suffered more severe disease and stay in a longer hospital. Our results showed that the age and the platelet level of patients were positively correlated with the length of stay-in hospital, which was consistent with previous results, while the lymphocyte level was negatively correlated with the length of in the hospital, which was in contrast to previous reports. The reason may be that the patient's condition was stable on admission, but they progressed further during treatment. In addition, it may be also related to the limited number of severe patients enrolled in this study. Routine changes in patients with COVID-19 are not the manifestations of common viral infection. Leukopenia, neutropenia and an increase in lymphocyte proportion are not significantly changed in patients with a conventional general viral infection, but the COVID-19 blood routine changes differently.

Previous studies have shown that severe infections, immune-related factors, and other factors cause secondary thrombocytopenia, such as DIC, TTP, and HLH, which are characterized by rapid platelet decline.[17] Through the observation of patients included, we found that platelets increased first and then decreased in severe patients during

TABLE 3 Relationship between platelet trends and various indicators during treatment

	Group A	Group B	Statistics	*P* value
Time of hospitalization, d	21.63 ± 4.07	14.50 ± 4.30	4.178 (*t*)	.001
Age	56.88 ± 6.24	48.18 ± 16.01	2.139 (*t*)	.041

Note: Group A, patients with platelet peak during treatment. Group B, patients without platelet peak during treatment.

TABLE 4 Relations between ΔPLR and various indicators

	ΔPLR statistics	*P* value
Time of hospitalization, d	0.413[a] (*R*)	.023
Severe patients or nonsevere patients	4.122 (*t*)	.000

Abbreviation: ΔPLR, platelet-to-lymphocyte ratio difference.
[a]The correlation is significant at the .05 level.

treatment and there were six patients with significantly increased platelets, who were generally older and had longer hospital stays. Therefore, we speculated that the changes in platelets in the treatment course may be correlated with the progression and prognosis of COVID-19.

The possible causes of platelet changes in COVID-19 patients were analyzed as follows: (a) coronavirus directly invaded hematopoietic cells or bone marrow stromal cells, leading to hematopoietic inhibition.[18] (b) Previous studies have shown that the lung may be one of the organs in which mature megakaryocytes release platelets and that thrombocytopenia in patients with SARS-CoV infection may be associated with lung damage.[19,20] Extensive alveolar damage both occurred in patients with COVID-19 and SARS, and lung tissue damage was induced by a viral infection and high flow of oxygen. Injury of lung tissue and pulmonary endothelial cells can lead to activation, aggregation, and retention of platelets in the lung, and the formation of thrombus at the injured site, which may lead to the depletion of platelets and megakaryocytes, resulting in decreased platelet production and increased consumption.[20,21] (c) Huang et al[22] believed that patients with COVID-19 had a large amount of IL-1,

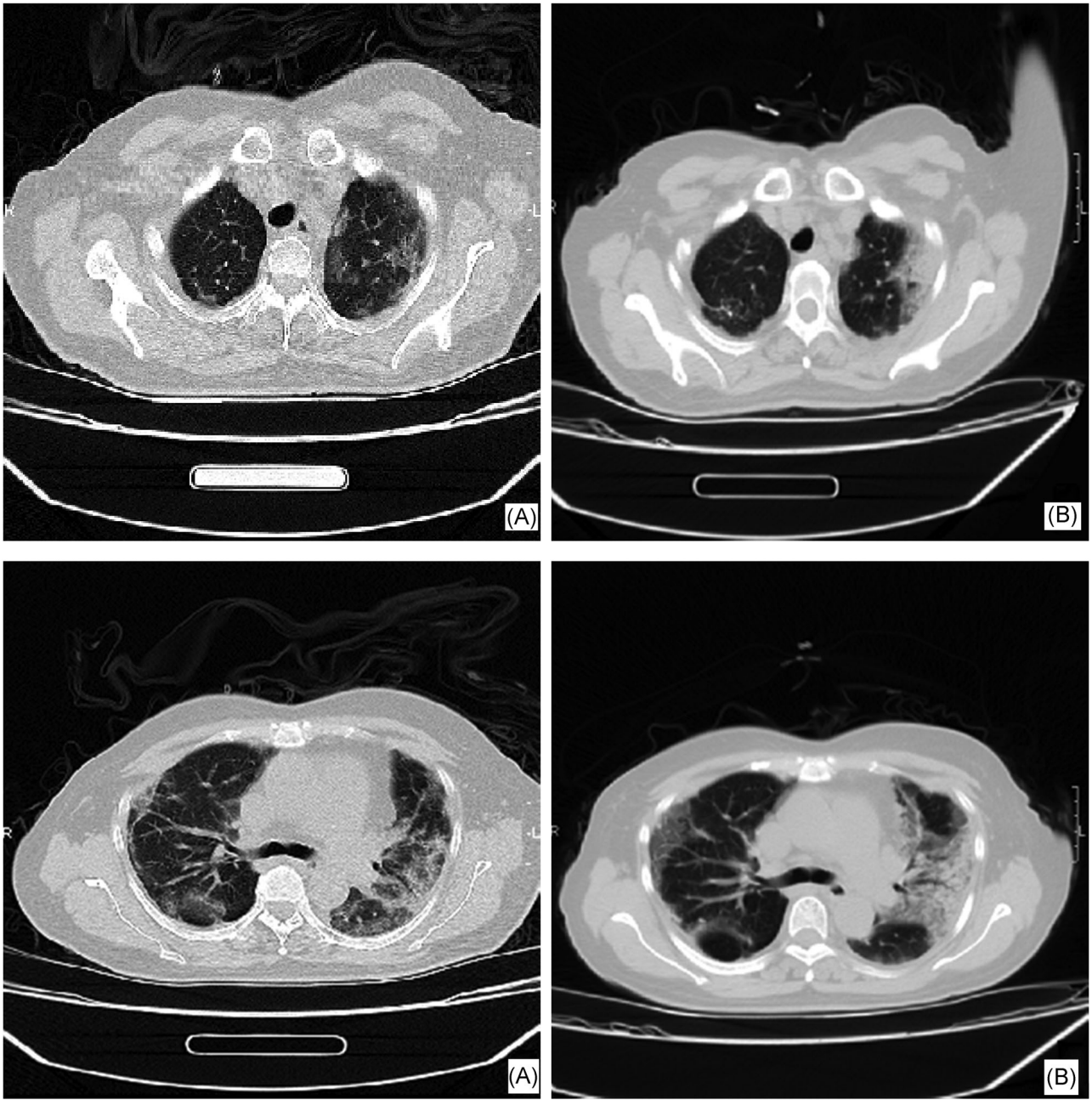

FIGURE 4 Pneumonitis worsens with platelet-to-lymphocyte ratio difference (ΔPLR) elevation in some patients. A, Before ΔPLR elevation. B, After ΔPLR elevation

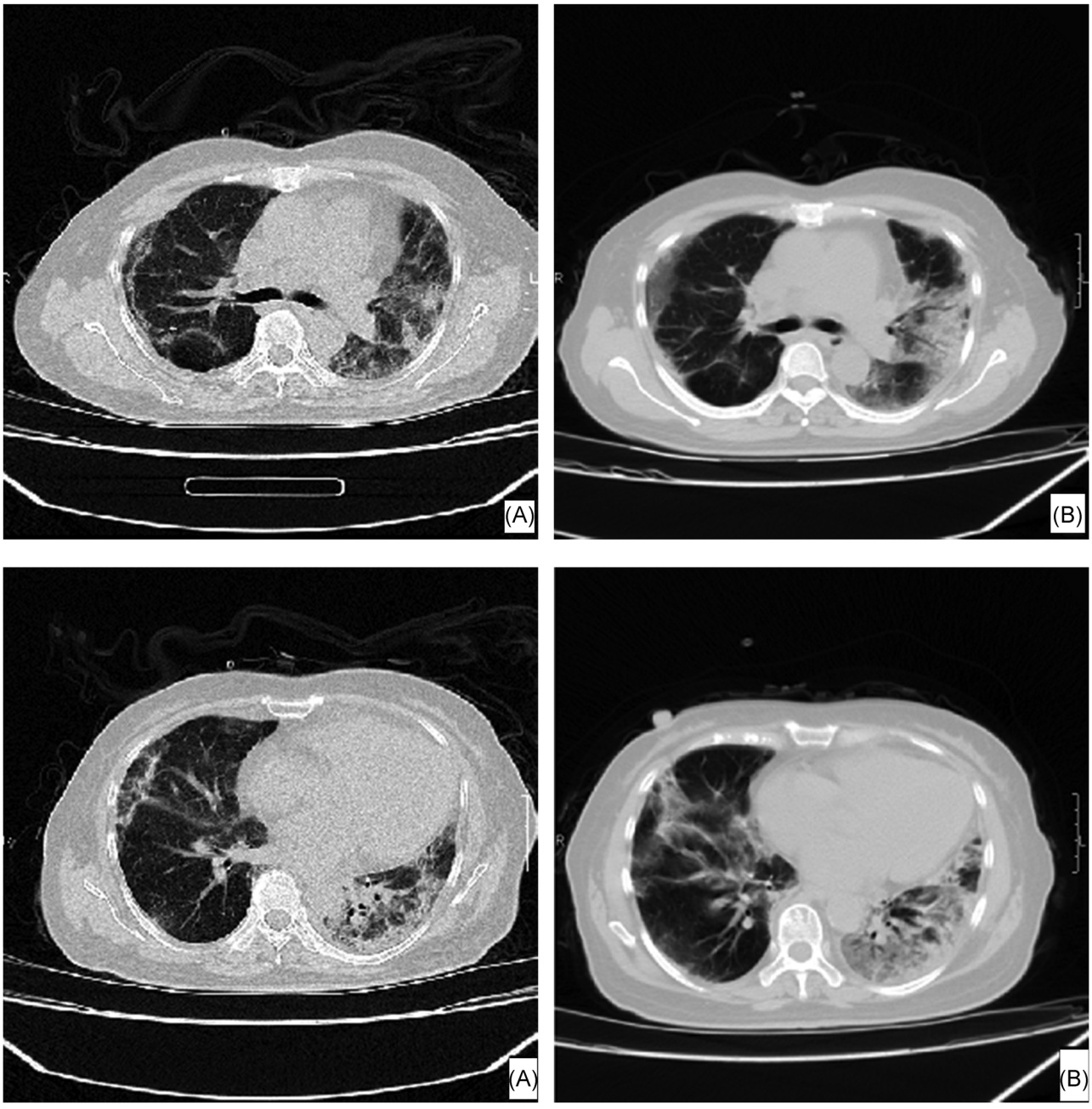

FIGURE 4 (Continued)

IFN-γ, IP-10, MCP-1, and other cytokines released, which may lead to Th1 activation. However, compared with nonsevere patients, severe cases had higher concentrations of cytokines such as G-CSF, IP-10, MCP-1, MIP-1, and TNF-α, suggesting that cytokine storm is related to the severity of the disease. However, unlike SARS-CoV infection, 2019-nCoV infection also causes increased secretion of Th2 cytokines that inhibit Th1, such as IL-4 and IL-10. In our results, in severe cases, the platelet significantly increased during treatment, which may be linked to the release of a large number of cytokines by the immune system. Infection with 2019-nCoV causes cytokine storms in body fluids, aggravating the patient's inflammatory response and stimulating the release of platelets, which often indicates a poor prognosis.[23,24] Of course, if the conditions permit, high-throughput cytokine detection for COVID-19 patients to judge whether they are over immune activated, it will be very convincing. However, because there is no 3P laboratory in the Huizhou area that can send such special infected blood samples for examination, so the testing for this item has to be abandoned. The difference is not founded from the analysis of simple blood routine numerical data. It is hoped that the future research direction is the correlation between blood routine changes and cytokines. The correlation between cytokine storm severity and prognosis may be one of the mechanisms of COVID-19, which is involved in the occurrence, development, and prognosis of COVID-19, providing a new idea for the treatment of

COVID-19.[25,26] However, there are many factors that affect platelet changes in the clinic. All patients in this study did not use invasive procedures such as tracheal intubation and deep vein catheterization. Therefore, the impact of invasive procedures on platelet changes was not considered in this article.[27] It can be seen from the foregoing that the use of hormones during the treatment of patients is not significantly different between severe and nonsevere patients, so their effects on platelets can also be ruled out.

As a new type of inflammation index, PLR mainly reflects the level of systemic inflammation. Previous studies have confirmed that PLR is closely related to tumors, diabetes, coronary heart disease, and connective tissue diseases, and the increase of PLR is related to tumor size, lymph node infiltration, distant metastasis and prognosis, and can be used as a potential inflammatory indicator for the clinical diagnosis of community-acquired pneumonia.[28] As an indicator of inflammation, PLR is mainly caused by megakaryocytes in bone marrow hematopoietic tissue and is a major participant in thrombosis. It plays a crucial role in the inflammatory response to recruit neutrophils and other inflammatory cells to the site of injury. PLT exists in an inactive form and can be activated quickly at the site of vascular injury, and can be rapidly activated in response to proinflammatory cytokine or infectious factors. The activation of platelets by this mechanism, even without any vascular damage, opens up new functions of platelets, namely inflammation and immune regulation, and the proinflammatory cytokine activity of PLT is mediated by its interaction with other leukocytes in the circulation, followed by the release of cytokines and chemokine to promote inflammation.[29] Lymphocytes are the main immune-active cells in the human body, and lymphocyte count is an early marker of physiological stress and systemic inflammation. Platelet-released platelet factor-4 can prevent agglutinin-A from inhibiting lymphocyte generation, and activated platelets enhance lymphocyte adhesion to the endothelium, thereby promoting lymphocyte homing in endothelial veins and migration to inflammatory sites. PLR refers to the ratio of the platelet-to-lymphocyte count. The advantage of PLR selection is that it reflects both aggregation and inflammatory pathways, and maybe more valuable in predicting various inflammations than platelet or lymphocyte counts alone.

The pathogenesis of COVID-19 is also related to the virus-induced inflammatory response in vivo.[30-32] According to the current clinical and relevant data, patients with lower lymphocyte levels at the first diagnosis are more seriously ill, and the progressive decline in lymphocyte proportion indicates a poor prognosis. According to prior analysis, we propose the PLR as an indicator which reflects the severity of inflammation in the process of treatment, by comparing the changes of PLR during treatment, we found that the higher the ΔPLR, the longer the hospital stay they were, of which showed a linear correlation. Therefore, we speculated that the changes in the platelet/lymphocyte ratio in peripheral blood during treatment could reflect the disease progression and prognosis of COVID-19 patients. The larger the ΔPLR, the more severe the cytokine storm, and the longer the hospital stay, the worse the prognosis. When ΔPLR increases in severe patients, we increase thymosin to regulate immune to elevate lymphocyte therapy to improve this situation, to prevent the development of severe patients or promote the improvement of symptoms in severe patients. After active symptomatic treatment, all three severe patients were successfully treated and successfully discharged from the hospital! The results of this treatment also seem to confirm our conjecture. We also calculated the cut-off value of ΔPLR. When ΔPLR > 126.7, we must actively intervene to prevent further deterioration of the disease. However, due to the lack of clinical data, this conclusion may be biased, and a larger number of samples are needed for further confirmation.

5 | CONCLUSION

Single-center case series of the 30 hospitalized patients with confirmed COVID-19 in Huizhou Municipal Central Hospital, presumed that the number of platelets and their dynamic changes during the treatment may have a suggestion on the severity and prognosis of the disease. The patient with markedly elevated platelets and longer average hospitalization days may be related to the cytokine storm. The PLR of patients means the degree of cytokine storm, which might provide a new indicator in the monitoring in patients with COVID-19.

CONFLICT OF INTERESTS

All authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTION

The authors of the manuscript declare contribution to the study.

ORCID

Zhi Guo http://orcid.org/0000-0003-2639-8216

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How to cite this article: Qu R, Ling Y, Zhang Y-h-z, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. *J Med Virol*. 2020;92:1533–1541. https://doi.org/10.1002/jmv.25767