European Review for Medical and Pharmacological Sciences 2020; 24: 12490-12499

Analysis of factors for disease progression in 61 patients with COVID-19 in Xiaogan, Hubei, China

Y. XING[1], H. WANG[2], X.-H. YAO[3], Y. LI[2], J.-T. HUANG[2], J. TANG[2], S. ZHU[2], Y.-Q. LIU[4], J. XIAO[2]

[1]Department of Clinical Laboratory, Chongqing University Center Hospital, Chongqing, China
[2]Department of Cardiovascular Medicine, Chongqing University Center Hospital, Chongqing, China
[3]Department of Medical Section, Traditional Chinese Medical Hospital of Dawu County, Dawu, Xiaogan, Hubei, China
[4]Department of Oncology and Hematology, Chongqing University Center Hospital, Chongqing, China

Yang Xing and Hao Wang contributed equally to this work

Abstract. – OBJECTIVE: The aim of this study was to retrospectively analyze clinical characteristics and laboratory results of the novel coronavirus pneumonia (COVID-19) patients so as to identify factors related to disease progression.

PATIENTS AND METHODS: Sixty-one patients with COVID-19 were divided into two groups: an improvement/stabilization group (n = 53) and a progression group (n = 8). Clinical data were collected to analyze and compare the differences between the two groups.

RESULTS: Of the sixty-one patients, thirty-one were male (50.8%), and thirty were female (49.2%), with a median age of 53 years. On admission, significant differences were observed between the two groups with respect to the levels of Creatine Kinase (CK), lymphocytes, D-dimer and creatinine, and prothrombin time (PT). Univariate logistic regression analysis showed that Platelet-to-lymphocyte ratio (PLR), lymphocytes, Mean platelet volume to lymphocyte ratio (MPVLR), CK, White Blood count to mean platelet volume ratio (WMR), Lymphocyte-to-monocyte ratio (LMR), and serum creatinine were important factors for disease progression. Multivariate logistic regression analysis showed that PLR was an independent factor for disease progression in COVID-19 patients. The receiver operating characteristic (ROC) curve revealed that the best predictor of disease progression was CK. Dynamic changes in the laboratory indicators of patients were tracked, and significant differences were found in the variation trends of white blood cell count, neutrophil count, and WMR, which gradually increased in the progression group, but gradually decreased in the improvement/stabilization group.

CONCLUSIONS: Risk factors for disease progression included PLR, lymphocytes, MPVLR, CK, WMR, LMR, and creatinine, among which, PLR is an independent risk factor for disease progression in COVID-19 patients.

Key Words:
2019 Novel coronavirus disease (COVID-19), Pneumonia, Clinical features, Prognostic indicator.

Abbreviations
AUC, Area under curve; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; CAR, C-reactive protein to albumin ratio; CK, Creatine Kinase; LMR, Lymphocyte-to-monocyte ratio; MPVLR, Mean platelet volume to lymphocyte ratio; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; PCT, procalcitonin; PT, prothrombin time; RT-PCR, real-time fluorescence reverse transcription-polymerase chain reaction; ROC, receiver operating characteristic; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SPSS; Statistical Package for the Social Sciences; WMR, White Blood count to mean platelet volume ratio.

Introduction

Currently, the COVID-19 pandemic is threatening global health. The infection rates outside China are increasing rapidly, with more than 2.18 million confirmed global cases of COVID-19, as of April 18, 2020. Most patients of COVID-19 have mild symptoms, but some may develop severe pneumonia, pulmonary edema, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome, or even death. According to an epidemiological report of COVID-19 by the

Corresponding Author: Jun Xiao, MD; e-mail: xj73wy@163.com
Co-*Corresponding Author:* Yunqi Liu, MD; e-mail: 413972530@qq.com

China Center for Disease Control (CDC), among a total of 44,672 confirmed cases, severe case patients accounted for 13.8%, and critically ill patients accounted for 4.7%[1]. For critically ill patients, the crude case fatality ratio was 49.0%, and the average risk of death within a 10-day follow-up was 0.325[1].

Huang et al[2] found that high body temperature, dyspnea symptoms, respiratory rate, white blood cell count, neutrophil count, lymphocyte count, D-dimer, albumin, and procalcitonin were risk factors for ICU care in COVID-19 patients. However, risk factors for the disease progression in COVID-19 patients have not been reported. To further improve the treatment of COVID-19 patients and reduce mortality, it is necessary to evaluate the possible risk factors for disease progression. Through a retrospective analysis of general data, clinical symptoms, and laboratory results of sixty-one confirmed COVID-19 patients admitted to the isolation wards of Dawu County Hospital of Traditional Chinese Medicine in Xiaogan city, Hubei province, China, we explored the possible risk factors for disease progression, so as to provide guidance for improving prognosis, and reducing the rate of severe disease and mortality.

Patients and Methods

Patients

A total of sixty-one patients with confirmed COVID-19, who were admitted to the isolated wards of Dawu County Hospital of Traditional Chinese Medicine in Xiaogan, Hubei province, China, between January 23, 2020, and March 11, 2020, were enrolled in our study. All the patients had confirmed diagnosis based on a positive test result for COVID-19 nucleic acids by real-time fluorescence reverse transcription-polymerase chain reaction (RT-PCR), according to the "Diagnosis and Treatment Protocol for Novel Coronavirus Infection-Induced Pneumonia version 7 (trial)"[3].

The study was performed in accordance with Chongqing University Center Hospital Ethics Committee [Ethics No. (16) 2020] (April 26, 2020). Verbal consent was provided by all the patients, but the requirement for written informed consent was waived, given the state of an emerging infectious disease.

Definitions

The patients were divided into the progression group or the improvement/stabilization group based on their clinical results. Specific criteria were as follows: (1) progression group: common-type disease developed to severe- or critical-type, or death; severe-type disease developed to critical-type or death; or critical-type disease progressed to death. (2) improvement/stabilization group: common-, severe-, and critical-types remained unchanged; severe-type changed to common-type; or critical-type changed to severe- or common-type.

The clinical typing was divided into four types according to the "Diagnosis and Treatment Protocol for Novel Coronavirus Infection-Induced Pneumonia version 7 (trial)"[3] by the general office of the National Health Commission of China: (I) mild type, with mild clinical symptoms, and no pneumonia on imaging; (II) common type, with fever, symptoms of the respiratory tract and other symptoms, and with pneumonia on imaging; (III) severe type, with any of the following conditions: 1) respiratory distress, RR $\geq$ 30 times/min; 2) at rest, oxygen saturation of arterial blood of finger $\leq$ 93%; 3) arterial oxygen partial pressure (PaO2/FiO2) $\leq$ 300 mmHg; (IV) critical type, with any of the following conditions: 1) respiratory failure and the need for mechanical ventilation; 2) shock; 3) with another organ failure which should be monitored and treated by ICU.

Research Methods

Age, gender, underlying diseases, clinical symptoms, and vital signs were retrospectively analyzed for patients in both groups upon admission. Also, blood test results were analyzed, which mainly included blood routine, liver function, renal function, coagulation function, myocardial enzyme spectrum, blood lipid, C-reactive protein (CRP), procalcitonin (PCT) and other possible markers of disease. Numerous previous studies[4-6] have reported that as new inflammatory markers, NLR, LMR, PLR, MPVLR, CAR, WMR, and other peripheral blood correlation parameter ratios might be of value in evaluating the severity of multiple systemic diseases, including infectious diseases; thus, we calculated the above ratios and compared the differences between the two patient groups.

Statistical Analysis

Categorical variables were described as frequency rates and percentages, and continuous variables were described as mean, median, and interquartile range (IQR) values. Independent group *t*-tests were used for comparing means for continuous variables when the data were normal-

ly distributed; otherwise, the Mann-Whitney test was used for comparison. χ^2 test was used to compare proportions for categorical variables, whereas Fisher's exact test was used when the data were limited. Univariate and multivariate logistic regression analyses were adopted to identify the risk factors for disease progression. All variables from the univariate analysis with a *p*-value <0.1 were subjected to the multivariate logistic regression analysis. The area under the curve (AUC) of receiver operating characteristic (ROC) curve was used to evaluate the predictive effect of factors on disease progression. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 26.0 software (IBM Corp., Armonk, NY, USA). For unadjusted comparisons, a 2-sided α of less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of sixty-one inpatients with confirmed COVID-19, which included thirty-one male (50.8%) and thirty female (49.2%) patients, of a median age of 53 years (IQR, 41-63 years; range, 30-85 years) were included in the study. Among the sixty-one patients, eighteen (29.5%) had one or more underlying diseases. Hypertension [12 (19.7%)], diabetes mellitus [6 (9.8%)] and cardiovascular disease [4 (6.6%)] were the most common underlying diseases (Table I).

The most common symptoms were fever [49 (80.3%)], cough [37 (60.7%)], fatigue [33 (54.1%)], dyspnea [21 (34.4%)] and myalgia [15 (24.6%)]. The less common symptoms were dizziness, headache, and diarrhea (Table I).

Compared with the improvement/stabilization group (n = 53), the progression group (n = 8) had a higher proportion of patients with underlying diseases (50% > 26.4%), patients who were more likely to experience cough (100% > 54.7%, $p = 0.018 < 0.05$) and patients with higher respiratory rate (median respiratory rate of 20 [IQR, 20-20] and 22 [IQR, 20-30], $p = 0.003 < 0.05$) (Table I).

Comparison of Laboratory Results Between the Two Groups

Significant differences were noted in laboratory results with respect to CK, lymphocytes, PT, D-dimer, and creatinine ($p = 0.007$, 0.011, 0.015, 0.035, and 0.041, respectively) between the progression and improvement/stabilization group

Table I. Baseline Characteristics of COVID-19 patients.

	Total (n = 61)	Improvement/ stabilization (n = 53)	Progression (n = 8)	*p*-value
Age, median (IQR), y	53 (41-63)	52 (41-63)	61 (40-67)	0.494
sex				
female	30 (49.2)	27 (49.1)	3 (37.5)	0.742
male	31 (50.8)	26 (50.9)	5 (62.5)	
Comorbidities	18 (29.5)	14 (26.4)	4 (50.0)	0.343
Hypertension	12 (19.7)	10 (18.9)	2 (25.0)	0.650
Cardiovascular disease	4 (6.6)	3 (5.7)	1 (12.5)	0.439
Diabetes mellitus	6 (9.8)	5 (9.4)	1 (12.5)	1.000
Malignancy	1 (1.6)	1 (1.9)	0	1.000
Chronic liver disease	1 (1.6)	1 (1.9)	0	1.000
Signs and symptoms				
Fever	49 (80.3)	43 (81.1)	6 (75.0)	0.650
Headache	11 (18.0)	10 (18.9)	1 (12.5)	1.000
Diarrhea	4 (6.6)	3 (5.7)	1 (12.5)	0.439
Myalgia	15 (24.6)	15 (28.3)	0	0.182
Cough	37 (60.7)	29 (54.7)	8 (100)	0.018
Fatigue	33 (54.1)	28 (52.8)	5 (62.5)	0.715
Dizziness	12 (19.7)	12 (22.6)	0	0.337
Dyspnea	21 (34.4)	17 (32.1)	4 (40)	0.429
Heart rate, median (IQR), bpm	85 (78-94)	85 (78-93)	88 (78-100)	0.448
Respiratory rate, median (IQR)	20 (20-21)	20 (20-20)	22 (20-30)	0.003
Mean arterial pressure, median (IQR), mmHg	93 (87-103)	95 (87-104)	88 (82-100)	0.203

Abbreviations: bpm, beats per minute; IQR, interquartile range. $p<0.05$ was considered statistically significant.

patients upon admission. The levels of CK, PT, and creatinine were higher, whereas the levels of lymphocytes and D-dimer were lower in the progression group compared to the improvement/stabilization group (Table II). In addition, comparison of NLR, LMR, PLR, MPVLR, CAR, WMR, and other peripheral blood correlation parameter ratios between the two groups showed that significant differences were found in the following four indicators: WMR, LMR, PLR, and MPVLR (p = 0.033, 0.031, 0.047, and 0.008, respectively). WMR and LMR were lower, and PLR and MPVLR were higher in the progression group compared with the improvement/stabilization group (Table II).

Results of a Logistic Regression Analysis of Risk Factors for Disease Progression in COVID-19 Patients

The results of a univariate logistic analysis showed that PLR (OR, 1.009; 95% CI: 1.002-1.015; p = 0.011), lymphocytes (OR, 0.109; 95% CI: 0.017-0.701; p = 0.020), MPVLR (OR, 1.123; 95% CI: 1.007-1.251; p = 0.037), CK (OR, 1.010;

Table II. Laboratory Findings of COVID-19 patients.

	Normal range	Total (n = 61)	Improvement/ stabilization (n = 53)	Progression (n = 8)	*p*-value
White blood count, $\times10^9$/L	4-10	5.40 (4.05-6.90)	5.42 (4.28-7.02)	3.81 (3.65-5.44)	0.065
Neutrophil count, $\times10^9$/L	1.8-6.3	3.39 (2.52-4.62)	3.45(2.57-4.92)	3.06 (2.24-4.09)	0.290
Monocyte count, $\times10^9$/L	0.1-0.6	0.39 (0.28-0.52)	0.40 (0.29-0.53)	0.30 (0.20-0.43)	0.114
Lymphocyte, $\times10^9$/L	1.1-3.2	1.28 (0.84-1.60)	1.32 (0.95-1.73)	0.715 (0.39-1.22)	0.011
Red blood cell distribution width,%	11-16	12.60 (12.20-14.15)	12.60 (12.20-14.15)	12.90 (12.43-14.00)	0.386
Platelet count, $\times10^9$/L	125-350	206.00 (157.50-251.50)	212.00 (163.00-252.00)	174.00 (135.50-239.00)	0.207
Mean platelet volume, fl	9-13	10.10 (9.05-10.95)	10.10 (9.00-10.95)	10.10 (9.70-11.60)	0.494
Prothrombin time, s	10.5-13.5	11.50 (10.60-12.30)	11.40 (10.60-12.30)	12.01 (12.03-15.55)	0.015
D-dimer, ng/mL	0-1.5	0.42 (0.15-12.30)	0.48 (0.19-0.96)	0.145 (0.043-0.44)	0.035
Total Protein, g/L	65-85	66.93 (62.61-71.71)	67.47 (62.61.71.77)	64.955 (62.89-69.63)	0.579
Albumin, g/L	40-55	37.80 (34.40-40.68)	37.80 (34.27-40.68)	38.675 (34.82-42.74)	0.572
Alanine aminotransferase, U/L	7-40	19.25 (11.00-28.95)	19.25 (11.09-28.58)	22.11 (6.75-32.45)	0.939
Aspartate aminotransferase, U/L	15-40	27.43 (19.67-34.69)	27.00 (18.58-35.57)	28.93 (22.19-35.68)	0.718
Alkaline phosphatase ,U/L	50-135	59.34 (48.98-72.93)	62.03 (49.09-78.51)	55 (48.51-59.34)	0.162
Total bilirubin, mmol/L	0-21	11.10 (7.78-13.31)	11.10 (7.73-13.40)	11.11 (8.50-13.29)	0.831
Blood urea nitrogen, mmol/L	3.1-8	3.86 (2.90-5.10)	3.74 (2.80-4.77)	5.345 (3.92-6.27)	0.050
Creatinine, µmol/L	57-97	63.63 (50.80-77.80)	62.60 (48.71-75.02)	75.98 (60.05-105.33)	0.041
Blood uric acid, µmol/L	89-357	269.00 (203.27-325.95)	269.00 (203.27-311.00)	270.77 (186.80-382.09)	0.825
Cystatin C, mg/L	0.51-1.09	1.00 (0.83-1.15)	0.96 (0.81-1.14)	1.04 (1.00-1.29)	0.198
Creatine kinase, U/L	24-195	56.75 (36.27-93.93)	50.38 (35.46-78.55)	127.70 (64.66-207.07)	0.007
Creatine kinase isoenzymes, U/L	0-24	9.90 (7.00-13.25)	9.90 (7.00-13.25)	9.52 (6.00-15.91)	0.854
Lactate dehydrogenase, U/L	120-250	200.00 (167.00-307.30)	188.00 (165.51-291.37)	246.87 (170.97-370.82)	0.172
C reactive protein, mg/L	0-5	15.56 (0.90-49.22)	7.22 (0.80-48.04)	27.18 (11.46-73.30)	0.057
Procalcitonin, µg/L	0-0.5	0.08 (0.05-0.23)	0.07 (0.05-0.20)	0.11 (0.07-0.26)	0.453
Neutrophil-to-lymphocyte ratio, NLR	NA	2.88 (1.94-5.05)	2.63 (1.89-4.55)	4.82 (2.70-8.26)	0.080
Lymphocyte-to-monocyte ratio, LMR	NA	3.20 (2.25-4.24)	3.47 (2.51-4.40)	2.46 (1.84-2.91)	0.031
Platelet-to-lymphocyte ratio, PLR	NA	170.07 (130.18-225.03)	168.52 (124.00-203.81)	302.92 (156.21-425.08)	0.047
Mean platelet volume to lymphocyte ratio, MPVLR	NA	7.65 (5.98-13.30)	7.46 (5.76-11.62)	16.41 (8.25-26.13)	0.008
C-reactive protein to albumin ratio, CAR	NA	0.48 (0.03-1.29)	0.43 (0.02-1.29)	0.70 (0.28-2.12)	0.115
White Blood count to mean platelet volume ratio, MR	NA	0.57 (0.40-0.74)	0.60 (0.44-0.74)	0.40 (0.24-0.54)	0.033

Abbreviations: IQR, interquartile range; NA, not available. p-values indicate differences between Improvement/stabilization and Progression patients. p<0 .05 was considered statistically significant.

Table III. Logistic analysis results of risk factors for disease progression.

Variables	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*	OR	95%CI	*p*
White blood count, $\times 10^9$/L	0.701	0.434-1.132	0.146			
Neutrophil count, $\times 10^9$/L	0.841	0.534-1.325	0.456			
Monocyte count, $\times 10^9$/L	0.013	0.000-3.488	0.129			
Lymphocyte, $\times 10^9$/L	0.109	0.017-0.701	0.020			
Red blood cell distribution width,%	1.014	0.597-1.722	0.959			
Platelet count, $\times 10^9$/L	0.993	0.980-1.005	0.246			
Mean platelet volume, fl	1.146	0.589-2.231	0.688			
Prothrombin time, s	0.997	0.927-1.072	0.930			
D-dimer, ng/mL	0.101	0.005-1.904	0.126			
Total Protein, g/L	0.973	0.870-1.088	0.630			
Albumin ,g/L	1.062	0.928-1.215	0.385			
Alanine aminotransferase ,U/L	1.002	0.985-1.020	0.799			
Aspartate aminotransferase ,U/L	0.994	0.930-1.064	0.873			
Alkaline phosphatase ,U/L	0.961	0.902-1.025	0.224			
Total bilirubin, mmol/L	0.966	0.831-1.123	0.653			
Blood urea nitrogen, ,mmol/L	1.163	0.840-1.612	0.363			
Creatinine, μmol/L	1.035	0.995-1.077	0.090			
Blood uric acid, μmol/L	1.163	0.840-1.612	0.363			
Cystatin C, mg/L	2.652	0.215-32.769	0.447			
Creatine kinase, U/L	1.010	1.001-1.02	0.038	1.011	0.998-1.024	0.090
Creatine kinase isoenzymes, U/L	0.983	0.871-1.109	0.779			
Lactate dehydrogenase, U/L	1.003	0.997-1.010	0.292			
C reactive protein, mg/L	1.011	0.993-1.029	0.241	1.054	0.982-1.132	0.147
Procalcitonin, μg/L	0.591	0.005-64.872	0.826			
Neutrophil-to-lymphocyte ratio, NLR	1.017	0.930-1.111	0.718			
Lymphocyte-to-monocyte ratio, LMR	0.515	0.254-1.046	0.066			
Platelet-to-lymphocyte ratio, PLR	1.009	1.002-1.015	0.011	1.013	1.001-1.024	0.033
Mean platelet volume to lymphocyte ratio, MPVLR	1.123	1.007-1.251	0.037			
C-reactive protein to albumin ratio, CAR	1.491	0.722-3.078	0.280			
White Blood count to mean platelet volume ratio, WMR	0.020	0.000-1.196	0.061	0.064	0.003-1.516	0.089

Abbreviations: OR, Odds Ratio; CI, Confidence interval.

95% CI: 1.001-1.02; $p = 0.038$), WMR (OR, 0.020; 95% CI: 0.000-1.196; $p = 0.061$), LMR (OR, 0.515; 95% CI: 0.254-1.046; $p = 0.066$) and creatinine (OR, 1.035; 95% CI: 0.995-1.077; $p = 0.090$) were significantly correlated with disease progression.

A p-value of <0.1 was used as the screening condition, and the correlated indicators were excluded. The indicators of the univariate logistic regression analysis, namely, PLR, CK, WMR, and creatinine, were subjected to the multivariate logistic regression analysis. The univariate logistic analysis resulted in the lowest p-value for PLR; thus, it was included, whereas lymphocytes, MPVLR, and LMR correlated with PLR, so they were excluded. The regression equation of the probability of patients in the progression group was obtained by using the enter method: probability =–8.731 + 0.011 × CK + 0.053 × creatinine + 0.013 × PLR - 2.742 × WMR. The results also suggested that PLR (OR, 1.103; 95% CI: 1.001-1.024; $p = 0.033$) was an independent risk factor for disease progression in COVID-19 patients (Table III).

The above logistic regression analysis showed that CK, creatinine, PLR, and WMR were important risk factors for disease progression, and ROC analysis was used to compare the effectiveness. The larger the PLR, CK, and creatinine values, the more likely was the disease to worsen. WMR was contrary to these three; therefore, the reciprocal of WMR was included in the ROC analysis. As shown in Figure 1 and Table IV, CK (AUC = 0.821, $p = 0.007$; Sensitivity, 100%; Specificity, 59.0%) was the best predictor of disease progression. The logistic regression analysis equation, which included CK, creatinine, PLR, and WMR, was better than the four factors alone in predicting disease progression (AUC = 0.934, $p < 0.001$; sensitivity, 85.7%; specificity, 89.7%).

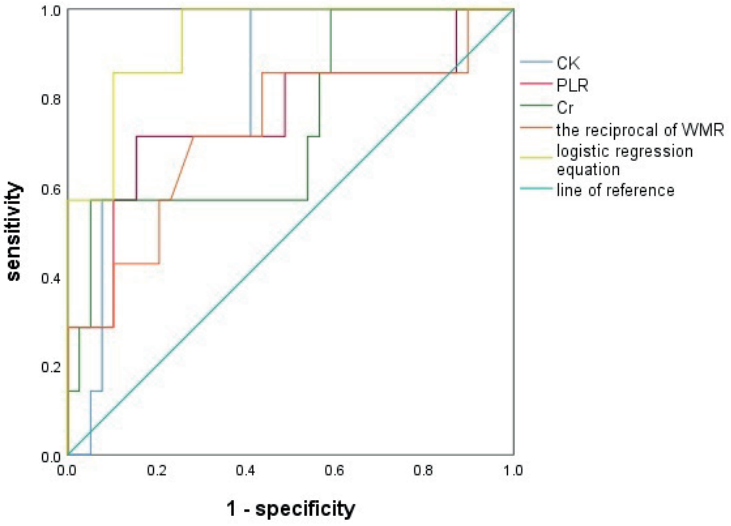

Figure 1. ROC analysis results of risk factors for Disease progression.

Table IV. ROC analysis results of risk factors for Disease progression.

	AUC	95%CI	*p*-value	Cut-off Value	Sensitivity	Specificity
CK	0.821	0.679-0.962	0.007	56.745	100%	59.0%
PLR	0.755	0.524-0.985	0.034	241.910	71.4%	84.6%
Cr	0.740	0.528-0.952	0.045	85.325	57.1%	94.9%
The reciprocal of WMR	0.729	0.500-0.958	0.056	2.198	71.4%	71.8%
logistic regression equation	0.934	0.852-1.000	<0.001	0.218	85.7%	89.7%

Abbreviations: CK, Creatine kinase; Cr, Creatinine; PLR, Platelet-to-lymphocyte ratio; WMR, White Blood count to mean platelet volume ratio; AUC, Area Under Curve; CI, Confidence interval.

Dynamic Characteristics of Laboratory Results of COVID-19 patients

In order to identify the main clinical characteristics of COVID-19 patients during disease progression, the test results from every seven days were conserved to make a group. From day 1 to day 21 after admission, the data collected were divided into five groups: the day 1 test group, the days 2-7 test group (the first week), the days 8-14 test group (the second week), the days 15-21 test group (the third week), and the days 22-28 test group (the fourth week). The dynamic changes of clinical laboratory indicators, including hematological and biochemical indicators, were tracked, and the median test results of the sixty-one patients were analyzed (Figure 2). During hospitalization, it was observed that there were significant differences in the variation trends of white blood cell count, neutrophil count, and WMR between the two groups, which gradually increased in the progression group, but gradually decreased in the improvement/stabilization group.

Discussion

Coronavirus disease 2019 (COVID-19) is a viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In some patients, the disease progresses rapidly causing a high risk of death. Understanding the risk factors for disease progression can help us in taking necessary measures in a timely manner so that the rapid progression of the disease can be prevented, prognosis can be improved, and mortality can be reduced.

A total of sixty-one inpatients with confirmed COVID-19 [eight in the progression group and fifty-three in the improvement/stabilization group; thirty-one male (50.8%) and thirty female (49.2%)], with a median age of 53 years (IQR, 41-63 years; range, 30-85 years) were enrolled in the study. Of the sixty-one patients, eighteen (29.5%) had one or more underlying diseases, among which hypertension [12 (19.7%)], diabetes [6 (9.8%)], and cardiovascular disease [4 (6.6%)] were the

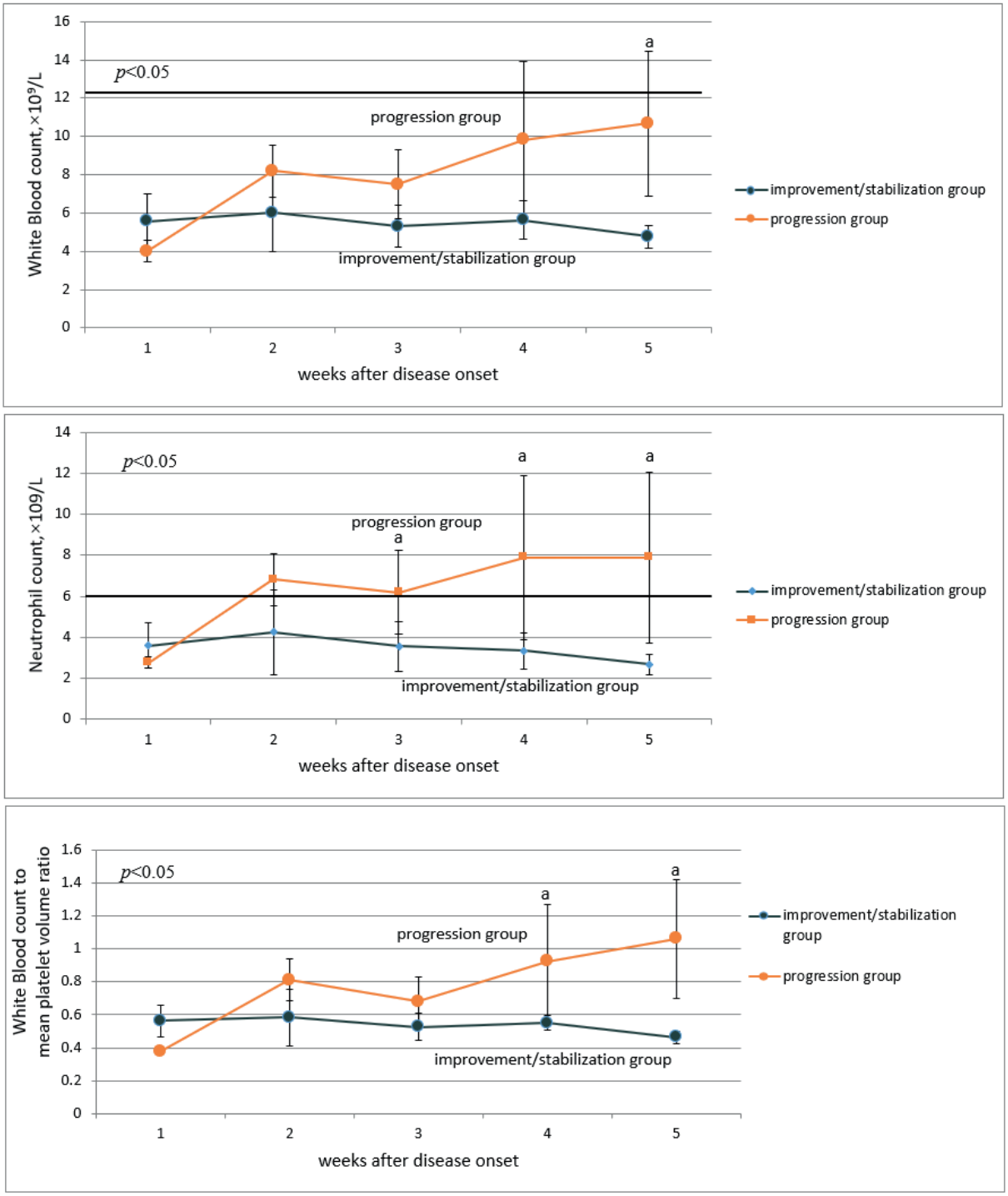

Figure 2. Dynamic Profile of Laboratory Parameters in 61 Patients with Corona Virus Disease 2019 (COVID-19). Timeline charts illustrate the laboratory parameters in 61 patients with COVID-19. 1-5 indicate the results in the first examination, the results in the first week, the results in the second week, the results in the third week, and the results in the fourth week. The solid lines in black show the normal upper limit of white blood count and Neutrophil count. [a]$p<0.05$ for progression group *vs.* improvement/stabilization group.

most common. Some studies have observed that COVID-19 is more common in males than females[7], and elderly males (> 60 years of age) with underlying diseases are more prone to develop acute respiratory distress syndrome (ARDS)[8]. It has also been reported that patients admitted to

ICU are older and have more complications than those not admitted to ICU, which indicates that advanced age and the presence of comorbidities might be risk factors for adverse outcomes, which in turn may be associated with gender. There were no statistically significant differences in age ($p = 0.494$), gender ($p = 0.742$), or underlying diseases ($p = 0.343$) between the two groups. The influence of these factors on disease progression and prognosis requires more elaborate observation and verification.

Our results revealed that the most common symptoms of inpatients with COVID-19 were fever [49 (80.3%)], cough [37 (60.7%)], asthenia [33 (54.1%)], dyspnea [21 (34.4%)], and myalgia [15 (24.6%)], whereas the less common symptoms were dizziness, headache, and diarrhea. Xu et al[9] studied sixty-two patients diagnosed with COVID-19, and found that the most common symptoms were fever in 48 cases (77%), cough in 50 cases (81%), cough in 35 cases (56%), headache in 21 cases (34%), myalgia or fatigue in 32 cases (52%), diarrhea in 3 cases (8%) and hemoptysis in 2 cases (3%), which was similar to our findings. We also found that compared with patients in the improvement/stabilization group, patients in the progression group were more likely to experience cough and higher respiratory rate. It has also been reported that the symptoms dyspnea, abdominal pain, and anorexia were more common in severe type patients than in non-ICU patients. It is possible that the onset of symptoms may be a helpful indicator for the identification of patients with poor prognosis[10].

In this study, the laboratory examination showed an increase in CK, PT, and creatinine, whereas a decrease in lymphocytes and D-dimer in the progression group compared with the improvement/stabilization group. A decrease in lymphocytes was the common characteristic found in COVID-19 patients, and it was speculated that SARS-CoV-2 might mainly affect lymphocytes, especially T lymphocytes. Virus particles spread through the respiratory mucosa and infect other cells, inducing cytokine storms *in vivo*, producing a series of immune responses and causing changes in peripheral leukocytes and immune cells (such as lymphocytes)[7]. Some patients rapidly developed ARDS and septic shock, resulting in multiple organ dysfunction and failure. As a result, patients in the progression group had lower lymphocytes and higher levels of CK, PT, and creatinine. Thus, early detection and timely treatment of critical cases are of crucial importance. D-dimer tends to increase in severe case-patients compared with ordinary patients[2,10,11]. This study suggested that D-dimer decreased in the progression group, which may not be reflected in the statistical analyses due to small sample size or low levels of D-dimer, and might be a risk factor for disease progression. However, this needs further observation and verification.

As new inflammatory markers, the ratios of peripheral blood-related parameters have predictive value for the prognosis of multiple diseases in multiple systems[4-6]. We compared NLR, LMR, PLR, MPVLR, CAR, and WMR between the two groups, and identified the following significant differences: while WMR and LMR were decreased, PLR and MPVLR were increased in the progressive group compared with the improvement/stabilization group. Among these markers, NLR and PLR have been reported to be correlated with the severity of COVID-19[12,13], whereas the ratios of other parameters were not reported in the analysis of COVID-19 patients.

In this research, a univariate logistic regression analysis showed that lymphocytes, CK, creatinine, PLR, MPVLR, WMR, and LMR were significantly correlated with disease progression. Previous studies have shown that SARS-CoV-2 infection may be related to cellular immunodeficiency, coagulation activation, myocardial injury, liver injury, and renal injury[10]. Our results suggested that early cellular immunodeficiency, myocardial injury, renal injury, and abnormal coagulation might be the risk factors for disease progression. Multivariate logistic regression analysis showed that PLR was an independent correlation factor in severe COVID-19 patients, which is consistent with the finding in a previous study on COVID-19 patients[13]. Further, an ROC analysis showed that when PLR > 241.910, the risk of disease progression was high, and the prognosis was poor.

PLR could play an important role as a new inflammatory diagnostic marker in disease progression and prognosis of various inflammatory diseases (such as tumors of various systems, COPD, pulmonary embolism, and pneumonia)[14-16]. Melsen et al[17] have shown that at the acute exacerbated stage of pneumonia, PLR increases with an aggravation of inflammation but the detailed mechanism is unknown. Platelets (PLT) have an essential role in the inflammatory response. They increase with the release of inflammatory cytokines, are rapidly activated in response to pro-inflammatory cytokines or infection factors, and

mediate the release of cytokines and chemokines through interactions with other leukocytes in the circulation to promote inflammation[18]. In addition, platelets are the main participants in thrombosis. Due to the patient's hypoxia state, the production of immature PLT may increase. Immature PLTs are more likely to aggregate, further aggravating the hypercoagulable and hyperviscosity state of patients. Under the common effect of inflammatory mediators, pulmonary microthrombus, and ischemic heart disease are likely to occur, thus endangering the patient's life[19]. Previous studies, as well as the present study, have consistently shown that most COVID-19 patients have decreased lymphocytes, which is related to the severity and prognosis of the disease[10]. This may be because SARS-CoV-2 mainly acts on lymphocytes, especially T lymphocytes. On the other hand, the platelet count is a marker of inflammation. PLR is the ratio of platelets to lymphocytes, which is useful not only in reflecting the activation of inflammatory pathways but also indicating coagulation and immune abnormalities. Therefore, compared with platelet or lymphocyte count alone, PLR is more predictive.

Based on the logistic regression analysis, ROC analysis with CK, creatinine, PLR, and MPVLR suggested that CK had the greatest impact on disease progression. The logistic regression equation, which included CK, creatinine, PLR, and MPVLR, was more accurate than the four markers alone in predicting disease progression. As mentioned earlier, the disease progression of COVID-19 may be caused by multiple factors, such as cellular immunodeficiency, coagulation abnormality, myocardial injury, and renal injury.

In addition, by tracking the dynamic changes of clinical laboratory indicators among the sixty-one patients, we found significant differences in the variation trends of white blood cell count, neutrophil count, and WMR between the two groups during hospitalization, which gradually increased in the progression group, but gradually decreased in the improvement/stabilization group. The increase in leukocyte and neutrophil count may be attributed to the cytokine storm caused by virus invasion; this inflammatory activation may lead to poor prognosis. The increase in WMR may be due to the fact that platelets with smaller volumes have higher sensitivity than platelets with normal and bigger volume and are more likely to be activated, leading to a higher risk of microthrombus.

The present study has a few limitations. Firstly, only sixty-one patients were enrolled, and such a small sample size may lead to the deviation of research results. Secondly, the patients were solely from the Dawu County Hospital of Traditional Chinese Medicine in Xiaogan city, Hubei province, China. Due to the lack of medical resources in the early stages, the number of patients with progressive disease may be higher than expected. Thirdly, this was a retrospective study, so some parameters were missing, which may also affect the final observations.

Conclusions

These results indicated that the risk factors for disease progression were PLR, lymphocytes, MPVLR, CK, WMR, LMR, and creatinine, among which, PLR was an independent risk factor for disease progression in COVID-19 patients. Currently, there is neither a known effective drug for treatment nor a vaccine available against COVID-19. Thus, it is necessary to strengthen the monitoring of the disease and prevent disease progression in order to reduce the rate of mortality.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

This study was partially supported by the Fundamental Research Funds for the Central Universities (Project No. 2020CDJYGRH-1003). We thank all patients involved in the study.

References

1) Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Chin J Epidemiol 2020; 41: 145-151.
2) Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fang, Xu J, Gu X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.
3) Diagnosis and treatment protocol for novel coronavirus pneumonia (7th interim edition). China NHCOTPSRO (2020-03-04).
4) Russell CD, Parajuli A, Gale HJ, Bulteel NS, Schuetz P, De Jager CPC, Loonen AJM, Merekoulias G, Baillie JK. The utility of peripheral blood leukocyte ratios as biomarkers in infectious diseases: A systematic review and meta-analysis. J Infect 2019; 78: 339-348.

5) Dragan D, Goran R, Maja S, Ivan S, Ivo U, Tamara A, Snjezana Z, Snezana M, Nikola S , Dzihan A. Neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume-to-platelet count ratio as biomarkers in critically ill and injured patients: which ratio to choose to predict outcome and nature of bacter. Mediators Inflammation 2018; 2018: 1-15.

6) Bozlu G, Karpuz D, Hallioglu O, Unal S , Kuyucu N. Relationship between mean platelet volume-to-lymphocyte ratio and coronary artery abnormalities in Kawasaki disease. Cardiol Young 2018; 28: 832-836.

7) Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507-513.

8) Liu W, Tao Z, Lei W, Mingli Y, Kui L, Ling Z, Shuang W, Yan D, Jing L , Liu H. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J 2020; 133: 1032-1038.

9) Xu X, Wu X, Jiang X, Xu K, YinG L, Ma C, Li S, Wang H, Zhang S, Gao H. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ 2020; 368: m606.

10) Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y. Clinical characteristics of 138 hospitalized patients with 2019 Novel Coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323: 1061-1069.

11) Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, Lang C, Huang D, Sun Q, Xiong Y, Huang X, Lv J, Luo Y, Shen L, Yang H, Huang G, Yang R. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol 2020; 92: 797-806.

12) Chan AS, Rout A. Use of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in COVID-19. J Clin Med Res. 2020; 12: 448-453.

13) Qu R, Ling Y, Zhang Y-H-Z, Wei L-Y, Chen X, Li X-M, Liu X-Y, Liu H-M, Guo Z, Ren H, Wang Q. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol 2020; 10.1002/jmv.25767.

14) Acharya S, Rai P, Hallikeri K, Anehosur V , Kale J. Preoperative platelet lymphocyte ratio is superior to neutrophil lymphocyte ratio to be used as predictive marker for lymph node metastasis in oral squamous cell carcinoma. J Investig. Clin Dent 2017; 8: e12219.

15) Karatas MB, Ipek G, Onuk T, Gungor B, Durmus G, Canga Y, Cakilli Y , Bolca O. Assessment of prognostic value of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in patients with pulmonary embolism. Acta Cardiol Sin 2016; 32: 313-320.

16) Karadeniz G, Aktogu S, Erer OF, Kir SB, Doruk S, Demir M, Sonat K. Predictive value of platelet-to-lymphocyte ratio in exacerbation of chronic obstructive pulmonary disease. Biomark Med 2016; 10: 701-710.

17) Melsen WG, Rovers MM, Groenwold RHH, Bergmans DCJJ, Camus C, Bauer TT, Hanisch E, Klarin B, Koeman M, Krueger WA. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. Lancet Infect Dis 2013; 13: 665-671.

18) Rayes J, BournE JH, Brill A, Watson SP. The dual role of platelet-innate immune cell interactions in thrombo-inflammation. Res Pract Thromb Haemostasis 2020; 4: 23-35.

19) Gunay E, Ulasli SS, Akar O, Ahsen A, Gunay S, Koyuncu T, Unlu M. Neutrophil-to-lymphocyte ratio in chronic obstructive pulmonary disease: a retrospective study. Inflammation 2014; 37: 374-380.