International Journal of Clinical Medicine, 2020, 11, 786-809
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

A Nomogram for Predicting the Severity of COVID-19 Using Laboratory Examination and CT Findings

Yani Kuang[1], Susu He[1], Shuangxiang Lin[1], Rui Zhu[1], Rongzhen Zhou[1], Jian Wang[1], Renzhan Li[2], Haiyong Lin[3], Zhibang Zhang[4], Peipei Pang[5], Wenbin Ji[1*]

[1]Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Wenzhou, China
[2]Sanmen People's Hospital, Taizhou, China
[3]Wenling First People's Hospital, Wenling, China
[4]Tiantai People's Hospital, Taizhou, China
[5]GE Healthcare, Hangzhou, China
Email: *13706551313@163.com, *wb.j@163.com

How to cite this paper: Kuang, Y.N., He, S.S., Lin, S.X., Zhu, R., Zhou, R.Z., Wang, J., Li, R.Z., Lin, H.Y., Zhang, Z.B., Pang, P.P. and Ji, W.B. (2020) A Nomogram for Predicting the Severity of COVID-19 Using Laboratory Examination and CT Findings. *International Journal of Clinical Medicine*, **11**, 786-809.
https://doi.org/10.4236/ijcm.2020.1112059

Received: November 30, 2020
Accepted: December 19, 2020
Published: December 22, 2020

Abstract

Background: The outbreak of COVID-19 has a significant impact on the health of people around the world. In the clinical condition of COVID-19, the condition of critical cases changes rapidly with a high mortality rate. Therefore, early prediction of disease severity and active intervention play an important role in the prognosis of severe patients. **Methods:** All the patients with COVID-19 in Taizhou city were retrospectively included and segregated into the non-severe and severe group according to the severity of the disease. The clinical manifestations, laboratory examination results, and imaging findings of the 2 groups were analyzed for comparing the differences between the 2 groups. Univariate and multivariate logistic regression were used for screening the factors that could predict the disease, and the nomogram was constructed. **Results:** A total of 143 laboratory-confirmed cases were included in the study, including 110 non-severe patients and 33 severe patients. The median age of patients was 47 years (range, 4 - 86 years). Fever (73.4%) and cough (63.6%) were the most common initial clinical symptoms. By using the method of multivariate logistic regression, the variables to construct nomogram include age (OR: 1.052, 95% CI: 1.020 - 1.086, $P = 0.001$), body temperature (OR: 2.252, 95% CI: 1.139 - 4.450, $P = 0.020$), lymphocyte count (OR: 1.128, 95% CI: 1.000 - 1.272, $P = 0.049$), ADA (OR: 1.163, 95% CI: 1.023 - 1.323, $P = 0.021$), PaO_2 (OR: 0.972, 95% CI: 0.953 - 0.992, $P = 0.007$), IL-10 (OR: 1.184, 95% CI: 1.037 - 1.351, $P = 0.012$), and bronchiectasis (OR: 3.818, 95% CI: 1.694 - 8.605, $P = 0.001$). The AUC of the established nomogram was 0.877. **Conclusions:** This study analyzed the cases of patients with COVID-19

in Taizhou city and constructed a model to predict the illness severity. When patients showed the features including older age, high body temperature, low lymphocyte count, low ADA value, low PaO_2, high IL-10, and bronchiectasis sign in CT predicts a greater likelihood of severe COVID-19.

Keywords

COVID-19, SARS-CoV-2, Clinical Characteristics, Severity Prediction

1. Background

In December 2019, the first pneumonia case of unknown origin was reported in Wuhan [1] [2] [3], the capital of China's Hubei province. The pathogen was identified as a new enveloped RNA betacoronavirus, which was considered to have developmental similarity with SARS-CoV [4]. The World Health Organization (WHO) named the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and named the resulting disease as coronavirus disease 2019 (COVID-19). Most of the infected individuals present with acute viral pneumonia, which spreads from person to person [5] [6] [7] [8].

In January 30, 2020, the WHO declared COVID-19 as the sixth public health emergency of international concern (PHEIC). As of March 6, 2020, there were 97,769 laboratory-confirmed cases worldwide [9]. The statistics of SARS-CoV (severe acute respiratory syndrome coronavirus), which appeared in 2003, reported 8422 infected people [10] [11]. In 2012, MERS-CoV (Middle East respiratory syndrome coronavirus) was prevalent only in the Middle East [12] [13] [14] [15]. However, COVID-19 has become a globally widespread disease [9] [16] [17], and the number of confirmed cases continues to rise [18].

According to the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (*Trial Version* 5), COVID-19 can be divided into 4 clinical types [19]. Clinical types are closely related to the prognosis of patients where critical-type patients develop acute symptoms and have a high mortality rate. At present, the severity of the disease is mainly based on patients' symptoms, laboratory examination, and CT performance, and then the clinicians make the adjustment of treatment measures. There are few methods and studies for the prediction of disease severity.

Hence, the purpose of this study was to predict the severity of COVID-19. We collected Taizhou all cure COVID-19 cases and retrospectively analysed the epidemiological characteristics, initial laboratory examination results, and CT images after hospitalisation. We aim to identify factors to construct a model for predicting the severity of COVID-19, for understanding the trend of disease progression in patients with newly diagnosed COVID-19, and for reducing the mortality and improving the prognosis of patients with a high risk of severe COVID-19.

2. Methods

2.1. Study Participants and Design

From January 17 to March 11, 2020, patients were consecutively enrolled in 4 hospitals in Taizhou city. The 4 hospitals include a municipal hospital and 3 county-level hospitals, namely the Taizhou Hospital Enze district, Wenling First People's Hospital, Sanmen People's Hospital, and Tiantai People's Hospital. All the patients were admitted after laboratory confirmation of SARS-CoV-2 infection. After diagnosis, all the patients were transferred to Taizhou Public Health Centre for isolation treatment, and the last patient was discharged from hospital on March 11, 2020 (the deadline for the study).

2.2. Data Source

We obtained electronic medical records and data of all the cured and discharged COVID-19 cases from the 4 hospitals from January 17 to March 11, 2020. The diagnostic criteria were positive result using qPCR detection of nasal swabs and pharyngeal swabs, which was carried out by using a Novel Coronavirus Real Time qPCR Kit, and processed according to the manufacturer's instructions (Shanghai ZJ Bio-Tech Co., Ltd). As all the confirmed diseases in Taizhou were treated at the public health centre of Enze district of Taizhou hospital, the medical records of some patients before admission were provided by the doctors from the respective hospitals. The cases from Wenling People's Hospital, Sanmen People's Hospital, and Tiantai People's Hospital were sent to the Taizhou Hospital researchers by the participants in the hospital. Only laboratory-confirmed cases were included in the study.

All clinical data were reviewed and extracted by a team of experienced respiratory clinicians in Taizhou hospital. The data were recorded in an Excel spreadsheet; if a data is missing, a request is made to the hospital where the participant is located, and the hospital participant then contacts the attending clinician. We extracted recent exposure history, clinical symptoms or signs, and laboratory examination results for admission from the electronic medical record. Imaging examinations included chest X-ray or computed tomography (CT) of the thorax. All the patients who underwent CT scanning were evaluated and reviewed by senior radiologists at Taizhou hospital. Any major differences between the 2 reviewers were resolved by discussion with the third panel of reviewers. All laboratory examinations were performed according to the patients' clinical care needs, including a complete blood count, blood chemical analysis, coagulation test, assessment of liver and kidney function as well as electrolytes, c-reactive protein (CRP), calcitonin, lactate dehydrogenase, lymphocyte factor assay, blood gas analysis, and creatine kinase measurements.

2.3. Study Definitions and Criteria

We segregated all the patients into severe group and non-severe group according to the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia* (*Trial*

Version 5) released by the National Health Commission & State Administration of Traditional Chinese Medicine [19]. The severe group included the serious and critical types, while the non-severe group included the mild and moderate types. The mild type was defined as having mild clinical symptoms with no signs of pneumonia based on imaging results. The moderate type was defined as having symptoms such as fever, respiratory tract symptoms, and the appearance of pneumonia based on imaging results. The serious type was defined based on the following conditions: 1) respiratory distress with respiratory rate (RR) > 30/min; 2) oxygen saturation < 93% at rest; and 3) arterial blood oxygen partial pressure ($Pa0_2$)/oxygen concentration ($Fi0_2$) < 300 mmHg (1 mmHg = 0.133 KPa). The critical type was defined based on any of the following conditions: 1) respiratory failure and the need for mechanical ventilation; 2) shock; and 3) organ failure that requires intensive care unit (ICU) care.

The date of exposure refers to the earliest date of exposure to a source of transmission (people in Wuhan or confirmed patients). The incubation period was defined as the time interval between the potential earliest date of exposure to the source of transmission and the earliest date of occurrence of symptoms (clinical symptoms such as cough and fever). The specific contact date (if the date was unclear, the case was excluded from the analysis) was recorded, and the incubation period was calculated based on the specific information of the exposure date. Treatment delay indicates the time between the onset of symptoms and hospitalisation. Body temperature under the armpit ≥37.5˚C was defined as fever.

2.4. Laboratory Confirmation

All cases were confirmed by the Zhejiang Center for Disease Control and Prevention (Zhejiang CDC). The nucleic acid extraction was carried out with the kit (Biogas, Nkilier Technology Co. LTD, Shenzhen, China) recommended by the Chinese Center for Disease Control and Prevention (China CDC). RT-PCR assays were performed in accordance with the protocol established by the WHO, and nucleic acid sequencing was performed using NGS (next-generation sequencing) technology.

2.5. Statistical Analysis

We used Microsoft corp. EXCEL, version 2019 (Microsoft Corporation, American), R software, version 3.5.2 (MathSoft company, American), and MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium), for data processing and analysis. Independent *t* sample test was used for comparing the difference between the 2 groups of continuous variables. The differences between the 2 groups were compared by the chi-square test or Fisher's exact test. Logistic regression analysis was performed on the indicators with statistically significant differences between the 2 groups ($P < 0.05$). The R software was used for generating the nomogram and MedCalc software was used for generating the receiver operating characteristic (ROC) curve. Test results with $P < 0.05$ was considered

statistically significant.

Ethical approval

The retrospective multicentre cohort study was approved by the ethics review committee of Taizhou Hospital, Sanmen People's Hospital, Wenling First People's Hospital, and Tiantai People's Hospital, and the written informed consent was waived.

3. Results

3.1. Demographic Characteristics of the Patients

As of March 11, 2020, a total of 146 confirmed patients in Taizhou were transferred to isolation hospitals and were discharged after the treatment. Three cases were not included in this study owing to the loss of the CT images of the first time on admission. We obtained basic information, clinical data, and CT images of 143 patients (96.6%), among whom 66 were women (46.2%), and 77 were men (53.8%). The demographic and clinical characteristics of the patients are shown in Table 1. On admission, the degree of severity of COVID-19 was categorized as non-severe in 110 patients and severe in 33 patients. Of all the patients, 60 patients (42.0%) had contacts with a confirmed patient, 70 (49.0%) had contacts with a person in the Wuhan area, 4 (2.8%) had contacts with both a confirmed patient and a person in the Wuhan area, and 9 (6.3%) had an unclear contact history. The median age of all the patients was 47 years (range, 4 - 86 years), 56.8% were aged 30 - 60 years. The median age of the non-severe patients was 44.5 years (range, 4 - 80 years), while the median age of the severe patients was 55.0 years (range, 27 - 86 years). 129 patients (90.2%) had a history of smoking, including 100 patients (90.9%) in the non-severe group and 29 patients (87.9%) in the severe group.

Table 1. Clinical characteristics of the study patients, according to disease severity.

	Overall (n = 143)	Non-severe (n = 110)	Severe (n = 33)
Age (years)			
Median (range)	47.0 (4 - 86)	44.5 (4 - 80)	55.0 (27 - 86)
<38	34 (23.8%)	31 (32.7%)	3 (0.9%)
38 - 48	43 (30%)	36 (32.7%)	7 (21.2%)
49 - 60	34 (23.8%)	26 (26.3%)	8 (24.2%)
>60	32 (22.4%)	17 (15.5%)	15 (45.5%)
Gander			
Female	66 (46.2%)	52 (47.3%)	14 (42.4%)
Male	77 (53.8%)	58 (52.7%)	19 (57.6%)
Smoking			
No	129 (90.2%)	100 (90.9%)	29 (87.9%)
Yes	13 (9.1%)	9 (8.2%)	4 (12.1%)
Unknown	1 (0.7%)	1 (0.9%)	0 (0%)

Continued

Contact history			
The history of contact with confirmed patients	60 (42.0%)	46 (41.8%)	14 (42.4%)
The history of contact with epidemic area	70 (49.0%)	54 (49.1%)	16 (48.5%)
Unknown	9 (6.3%)	6 (5.5%)	3 (9.1%)
Both	4 (2.8%)	4 (3.6%)	0 (0%)
Temperature (˚C)			
<37.5	1 (0.7%)	1 (0.9%)	0 (0%)
37.5 - 38	7 (4.9%)	7 (6.4%)	0 (0%)
38 - 38.5	39 (27.3%)	29 (26.4%)	10 (30.3%)
38.5 - 39	26 (18.2%)	19 (17.3%)	7 (21.2%)
39 - 40	32 (22.4%)	20 (18.2%)	12 (36.4%)
>40	1 (0.7%)	1 (0.9%)	0 (0%)
Unknown	37 (25.9%)	33 (30.0%)	4 (12.1%)
Clinical symptoms			
Fever	105 (73.4%)	76 (53.1%)	29 (20.1%)
Coughing of phlegm	41 (28.7%)	30 (27.3%)	11 (33.3%)
Dry cough	42 (29.4%)	30 (27.3%)	12 (36.4%)
Yellow sputum	8 (5.6%)	6 (5.5%)	2 (6.1%)
Sore throat	15 (10.5%)	12 (10.9%)	3 (9.1%)
Nasal obstruction	8 (5.6%)	8 (7.3%)	0 (0%)
Muscle soreness	14 (9.8%)	11 (10.0%)	3 (9.1%)
Weak	37 (25.9%)	31 (28.2%)	6 (18.2%)
Chest distress	25 (17.5%)	17 (15.5%)	8 (24.2%)
Coexisting disorders			
hypertension	20 (14.0%)	15 (13.6%)	5 (15.2%)
diabetes	12 (8.4%)	7 (6.4%)	5 (15.2%)
COPD	3 (2.1%)	2 (1.8%)	1 (3.0%)
The incubation period (days)			
<3	3 (2.1%)	3 (2.7%)	0 (0%)
3 - 6	10 (7%)	9 (7.3%)	1 (3.0%)
6 - 9	10 (7%)	9 (8.1%)	1 (3.0%)
9 - 12	6 (4.2%)	3 (2.7%)	3 (9.1%)
>15	4 (2.8%)	4 (3.6%)	0 (0%)
Unknown	110 (76.9%)	82 (74.5%)	28 (84.8%)
Treatment delay			
<1	49 (34.3%)	8 (24.2%)	41 (37.3%)
1 - 2	40 (28.0%)	8 (24.2%)	32 (29.1%)
2 - 5	22 (15.4%)	6 (18.2%)	16 (14.5%)
5 - 10	16 (11.2%)	7 (21.2%)	9 (8.2%)
>10	2 (1.4%)	2 (6.1%)	0 (0%)
Unknown	14 (9.8%)	2 (6.1%)	12 (10.9%)

The mean incubation period was 6.9 days (standard deviation [SD], 3.472 days), and the mean treatment delay period was 3.0 days (SD, 2.631 days). Fever (73.4%) was the most common symptom. A total of 91 patients (63.6%) developed cough: sputum (28.7%), yellow sputum (5.6%), and dry cough (29.4%). Sore throat (10.5%), nasal congestion (5.6%), muscle soreness (9.8%), and chest tightness (17.5%) were relatively few. Of all the patients, 24.5% had at least one coexisting illness (hypertension and/or chronic obstructive pulmonary disease). The average body temperature of the patients was 38.0˚C (range, 37˚C - 39˚C; SD, 3.741˚C), and only 1 case (0.7%) had a high fever (>40˚C).

3.2. Laboratory Examination Results of the Two Groups

As some of the patients were first admitted to the county hospital, some laboratory tests were not carried out owing to the conditions. A total of 123 cases was included for the analysis of laboratory examination results, and those without such examination were recorded as UNKOWN. There were 28 cases in the severe group and 95 cases in the non-severe group. Table 2 shows the details of the laboratory results of all the cases. In the non-severe group, except for the increase in blood glucose level (14 ± 60 mmol/L), the decrease of serum albumin (39 ± 5.2 g/L), erythrocyte sedimentation rate (35 ± 24 μmol/L), and serum sodium (130 ± 25 mmol/L), and the increase of CRP (15 ± 19 mg/L) and amyloid A (190 ± 330 mg/L) were observed. All other test results were within the normal range (Table 2).

Table 2. Laboratory findings of patients with COVID-19 on admission to hospital.

	Normal Range	Overall (n = 123)	Non-Severe (n = 95)	Severe (n = 28)
Lymphocyte count, $\times 10^9$/L	1.1 - 3.2	1.2 (±0.52)	1.3 (±0.52)	0.91 (±0.43)
$<1.1 \times 10^9$		43 (34.96%)	27 (28.42%)	16 (57.14%)
$1.1 - 3.2 \times 10^9$		67 (54.47%)	60 (63.16%)	7 (25%)
unknown		13 (10.57%)	8 (8.42%)	5 (17.86%)
Erythrocyte sedimentation rate (ESR), umol/L	59 - 104	38 (±24)	35 (±24)	47 (±24)
<59		68 (55%)	56 (59%)	12 (43%)
59 - 104		12 (10%)	8 (8%)	4 (14%)
Unknown		43 (35%)	31 (33%)	12 (43%)
Blood glucose, mmol/L	3.9 - 6.11	13 (± 53)	14 (± 60)	9.1 (± 5.1)
3.9 - 6.11		44 (36%)	36 (38%)	8 (29%)
>6.11		62 (50%)	47 (49%)	15 (54%)
Unknown		17 (14%)	12 (13%)	5 (18%)
Aspartate aminotransferase, U/L	15 - 40	30 (±17)	26 (±11)	40 (±28)
15 - 40		91 (74.0%)	73 (80.2%)	18 (19.8%)
>40		17 (13.8%)	10 (57.8%)	7 (42.2%)

Continued

Creatine kinase (CK), U/L	38 - 285	99 (±93)	83 (±69)	150 (±130)
38 - 285		85 (69%)	68 (72%)	17 (61%)
>285		13 (11%)	9 (9%)	4 (14%)
Unknown		25 (20%)	18 (19%)	7 (25%)
ADA, U/L	<20	13 (±3.6)	13 (±3.5)	15 (±3.8)
Lactic acid dehydrogenase, U/L	80 - 285	240 (±140)	200 (±100)	350 (±180)
80 - 285		72 (59%)	65 (68%)	7 (25%)
>285		21 (17%)	8 (8%)	13 (46%)
Unknown		30 (24%)	22 (23%)	8 (29%)
Albumin, g/L	40 - 55	38 (±5.2)	39 (±5.2)	35 (±4.0)
<40		16 (13%)	9 (9%)	7 (25%)
40 - 55		31 (25%)	29 (31%)	2 (7%)
Unknown		76 (62%)	57 (60%)	19 (68%)
Na, mmol/L	137 - 147	130 (±22)	130 (±25)	140 (±3.7)
<137		37 (30%)	29 (31%)	8 (29%)
137 - 147		69 (56%)	54 (57%)	15 (54%)
Unknown		17 (14%)	12 (13%)	5 (18%)
Mg, mmol/L	0.75 - 1.02	3.8 (±17)	4.7 (±19)	0.89 (±0.096)
<0.75		10 (8%)	8 (8%)	2 (7%)
CRP, mg/L	<8	20 (±24)	15 (±19)	35 (±31)
0 - 8		51 (41%)	44 (46%)	7 (25%)
>8		51 (41%)	36 (38%)	15 (54%)
Unknown		21 (17%)	15 (16%)	6 (21%)
Glomerular filtration rate (GFR), ml/min	NA	91 (±21)	94 (±19)	82 (±26)
Amyloid A	0 - 10	250 (±360)	190 (±330)	430 (±420)
0 - 10		21 (17%)	19 (20%)	2 (7%)
>10		79 (64%)	59 (62%)	20 (74%)
fibrinogen, s	2.0 - 4.0	3.9 (±1.4)	3.7 (±1.4)	4.5 (±1.3)
>4		30 (24%)	17 (18%)	13 (46%)
0 - 4		60 (49%)	51 (54%)	9 (32%)
D dimer level, g/L	0 - 0.5	0.40 (±0.59)	0.35 (±0.58)	0.54 (±0.63)
PaO_2, mmHg	83 - 108	94 (±31)	99 (±33)	83 (±24)
<83		36 (29%)	23 (24%)	13 (46%)
83 - 108		35 (28%)	28 (29%)	7 (25%)
>108		21 (17%)	18 (19%)	3 (11%)
Unknown		31 (25%)	26 (27%)	5 (18%)
Oxygen concentration, %	NA	26 (±13)	25 (±14)	27 (±11)
0 - 21		61 (50%)	51 (54%)	10 (36%)

Continued

>21		31 (25%)	18 (19%)	13 (46%)
Unknown		31 (25%)	26 (27%)	5 (18%)
Myoglobin, ng/ml,	12 - 75	46 (±56)	35 (±41)	84 (±80)
<12		7 (6%)	6 (6%)	1 (4%)
12 - 75		54 (44%)	45 (47%)	9 (32%)
>75		12 (10%)	5 (5%)	7 (25%)
IL-10, pg/ml	0.1 - 5.0	5.2 (±5.2)	4.0 (±2.5)	9.4 (±9.2)
0 - 5		56 (46%)	49 (52%)	7 (25%)
>5		28 (23%)	17 (18%)	11 (39%)
CD3 absolute value, /uL	770 - 2041	720 (±450)	790 (±460)	490 (±330)
<770		28 (23%)	19 (20%)	9 (32%)
770 - 2041		17 (14%)	15 (16%)	2 (7%)
CD4 absolute value, /μL	414 - 1123	440 (±260)	490 (±260)	290 (±200)
<414		26 (21%)	18 (19%)	8 (29%)
414 - 1123		19 (15%)	16 (17%)	3 (11%)
CD8 absolute value--/μL	238 - 874	290 (±180)	330 (±180)	190 (±130)
<238		22 (18%)	15 (16%)	7 (25%)
238 - 874		23 (19%)	19 (20%)	4 (14%)

In the severe group, following parameters showed a decreased value: lymphocyte count decreased ((0.91 ± 0.43) $\times 10^9$), erythrocyte sedimentation rate (38 ± 24 μmol/L), serum albumin (130 ± 25 g/L), glomerular filtration rate (82 ± 26 mL/min), arterial blood oxygen partial pressure (83 (± 24) mmHg), calcitonin level (0.086 ± 0.090 μg/L), total CD3 value (56 ± 13%), absolute CD4 value (290 ± 200/μL), and absolute CD8 value (190 ± 130/μL). Following parameters showed an increased value in the severe group: blood glucose level (13 ± 53 mmol/L), lactate dehydrogenase level (350 ± 180 U/L), CPR level (35 ± 31 mg/L), amyloid protein A level (430 ± 420), fibrinogen detection value (4.5 ± 1.3 s), D dimmer level (0.54 ± 0.63 g/L), pH level (7.8 ± 2.0), myoglobin (84 ± 80 ng/mL), IL-10 (9.4 ± 9.2 pg/mL), C1q (240 ± 38 mg/L), PT (16 ± 19 s), absolute CD3 value (490 ± 330/μL). Other test results were within the normal range.

3.3. CT Manifestations of the Two Groups

Five (3%) CT images could not be evaluated owing to poor respiratory artefact quality. CT images of 138 (97%) patients at admission were obtained. Among them, 34 patients were severe (31%) and 104 patients were non-severe (75%). The CT findings of the two groups of cases are shown in Table 3. Lesions in 135 patients (98%) were mainly distributed in the external or subpleural of the lung; 37 patients (27%), middle or inner zone of lung; and 34 patients (25%), both. Among them, the lesions in the middle or inner band of the lungs were more

Table 3. CT Manifestations of patients infected with COVID-19 admission to hospital.

	Overall	Non-Severe	Severe	*P*-value
	(n = 138)	(n = 104)	(n = 34)	
Peripheral or subpleural	135 (98%)	102 (98%)	33 (97%)	
Middle or inner band	37 (27%)	21 (20%)	16 (47%)	0.00441
both	34 (25%)	19 (18.3)	15 (44%)	
Shape				
Paving stone shape	21 (32%)	15 (15%)	6 (18%)	
Mass	51 (81%)	35 (34%)	16 (47%)	
Patchy	24 (40%)	16 (16%)	8 (24%)	
Strip shape	7 (9%)	6 (6%)	1 (3%)	
Honeycomb shape	8 (12%)	6 (6%)	2 (6%)	
Small patchy	58 (68%)	52 (50%)	6 (18%)	
Lung segment shape	4 (12%)	0	4 (12%)	
Irregular	4 (12%)	0	4 (12%)	
Nodular	4 (3.88%)	4 (3.88%)	0	
Ground glass density	37 (27%)	30 (29%)	7 (21%)	0.325
Mixed Density	87 (63%)	62 (60%)	25 (74%)	
Solid Density	14 (10%)	12 (12%)	2 (6%)	
The edge				
clear	21 (15%)	16 (15%)	5 (15%)	
unclear	117 (85%)	88 (85%)	29 (85%)	
CT signs				
consolidation	66 (48%)	43 (41%)	23 (68%)	0.0136
bronchial inflation	63 (46%)	43 (41%)	20 (59%)	0.0015
Bronchiectasis	65 (47%)	41 (39%)	24 (71%)	0.00305
Blood vessels penetrated the lesion	57 (41%)	42 (40%)	15 (44%)	0.855
distribution along the vascular bundle	83 (60%)	64 (62%)	19 (56%)	0.702
Adjacent vascular widening	72 (52%)	55 (53%)	17 (50%)	0.925
Septal thickening	58 (42%)	41 (39%)	17 (50%)	0.376
Fibrosis	42 (30%)	29 (28%)	13 (38%)	0.081
Accompanying signs				
Cavity or calcification				
Non	137 (99%)	103 (99%)	34 (100%)	
Yes	1 (1%)	1 (1%)	0 (0%)	
Lymphadenectasis				
Non	134 (97%)	102 (98%)	32 (94%)	0.545
Yes	4 (3%)	2 (2%)	2 (6%)	

Continued

Pleural effusion				
Non	135 (98%)	103 (99%)	32 (94%)	0.303
Yes	3 (2%)	1 (1%)	2 (6%)	
Chronic bronchitis				
Non	132 (96%)	100 (96%)	32 (94%)	0.983
Yes	6 (4%)	4 (4%)	2 (6%)	
Emphysema or Pulmonary bullous				
Non	133 (96%)	101 (97%)	32 (94%)	0.777
Yes	5 (4%)	3 (3%)	2 (6%)	

commonly observed in the severe patients (47% vs 20%). Mass (81%) was the most common lesion shape followed by patchy (68%). Irregularity in the shapes of the lung segments was observed only in severe patients, while the nodular shape was observed only in non-severe patients. Most of the lesions presented with mixed density (63%).

In 60% of the CT images, the lesion was distributed along the pulmonary bronchial tree, and in 62% of the CT images, the lesion was adjacent to vasodilation. Fifty-two percent of the CT images showed interlobular septal thickening, and 30% of the CT images showed fibrous foci. Other concomitant signs such as cavitation or calcification (1%), enlarged lymph nodes (3%), pleural effusion (2%), chronic bronchitis (4%), emphysema, or pulmonary bullous (4%) were rare. Consolidation (68% vs 41%), bronchial inflation signs (59% vs 41%), and bronchiectasis (71% vs 39%) were more common in the severe group.

3.4. Results of Univariate Logistic Regression Analysis Predicting the Severity of COVID-19 Patients

Univariate logistic regression was performed for all the collected variables, and the results are shown in Table 4. For all the factors such as clinical characteristics, laboratory results, and CT findings, the variables associated with the severity of COVID-19 were age (Odds ratio [OR]: 1.052, 95% confidence interval [CI]: 1.020 - 1.086, $P = 0.001$), days from the symptom onset to hospitalisation (OR: 1.213, 95% CI: 1.034 - 1.939, $P = 0.016$), days from the symptom onset to diagnosis (OR: 1.213, 95% CI: 1.084 - 1.357, $P < 0.001$), body temperature (OR: 2.252, 95% CI: 1.139 - 4.450, $P = 0.020$), Neutrophil count (OR: 0.087, 95% CI: 0.026 - 0.274, $P < 0.001$), Lymphocyte count (OR: 1.128, 95% CI: 1.000 - 1.272, $P = 0.049$), IgM (OR: 2.226, 95% CI: 1.015 - 4.883, $P = 0.046$), ADA (OR: 1.163, 95% CI: 1.023 - 1.323, $P = 0.021$), albumin (OR: 0.847, 95% CI: 0.725 - 0.988, $P <0.035$), CRP (OR: 1.024, 95% CI: 1.007 - 1.042, $P = 0.006$), Glomerular filtration rate (OR: 0.965, 95% CI: 0.942 - 0.988, $P = 0.004$), amyloid A (OR: 1.002, 95% CI: 1.001 - 1.003, $P = 0.001$), PCT (OR: 1.43E+11, 95% CI: 1334.315 - 1.53E+19, $P = 0.006$), PaO_2 (OR: 0.972, 95% CI: 0.953 - 0.992, $P = 0.007$), oxygen concentration (OR: 1.027, 95% CI: 1.001 - 1.053, $P = 0.044$), oxygenation index (OR:

Table 4. Univariate logistic regression results predicting severity of COVID-19.

Variable	Odds Ratio	Lower	Upper	*P* value
Age	1.052397	1.019954	1.085873	0.001391
Gender	0.716981	0.33105	1.552824	0.398768
Smoke	1.448029	0.417094	5.027131	0.559917
Contact1	0.9	0.417764	1.938894	0.787878
Contact2	0.882353	0.411933	1.889984	0.747415
Days1	1.195852	1.033785	1.383326	0.016078
Days2	1.212778	1.083784	1.357125	7.73E−04
Fever	2.646341	0.858115	8.161055	0.09033
Temperature	2.25173	1.139284	4.450414	0.019538
Days3	1.115935	0.966888	1.287958	0.133713
Cough	1.710616	0.707724	4.134677	0.233169
Sputum	1.222222	0.534092	2.79695	0.634723
Sore Throat	0.765625	0.203181	2.885017	0.693161
Nasal Congestion	6.85E−08	0	Inf	0.99059
Muscle Soreness	0.84375	0.221514	3.213852	0.803366
Weak	0.551724	0.208304	1.461324	0.23144
Chest Congestion	1.893665	0.756532	4.740007	0.172581
Diarrhea	1.053763	0.316912	3.503867	0.931923
Headache	2.125	0.646991	6.979424	0.214117
Dizziness	0.9375	0.242985	3.617126	0.925361
Basic Diseases	1.118012	0.499822	2.500796	0.785943
Hypertension	1.055556	0.35412	3.146385	0.922706
Diabetes	2.452381	0.725797	8.286306	0.148723
WBC	1.114387	0.981275	1.265557	0.095174
RBC	0.687443	0.323418	1.461197	0.329977
Hb	0.986271	0.961506	1.011673	0.286656
Hematocrit	1.011476	0.980254	1.043694	0.475669
PLT	0.997789	0.991605	1.004012	0.485326
L	0.086924	0.02757	0.274063	3.06E−05
Ratio of Monocytes	0.141741	0.004924	4.080115	0.254407
N	1.128092	1.00055	1.271893	0.04896
ESR	1.0164	0.997625	1.035529	0.087266
Creatinine	1.014157	0.995714	1.032941	0.133283
Urea	1.020293	0.956143	1.088747	0.544277
BG	0.997512	0.98417	1.011034	0.716888
ALT	1.008354	0.991145	1.025861	0.343522

Continued

Creatine Kinase	1.031699	1.003659	1.060524	0.026436
LAD	1.004959	1.00054	1.009396	0.027792
LDH	1.009157	1.003211	1.015139	0.002501
IgG	0.99228	0.948544	1.038034	0.736158
IgA	0.587786	0.328416	1.051995	0.073569
IgM	2.226405	1.015156	4.882874	0.04577
C3	0.525075	0.076438	3.606887	0.512329
C4	11.63921	0.51351	263.8143	0.12322
ADA	1.163198	1.022728	1.322962	0.021323
Triglyceride	1.008518	0.635767	1.599814	0.971257
Total Cholesterol	0.952982	0.731007	1.24236	0.721871
Albumin	0.84665	0.725305	0.988296	0.034934
Total Bilirubin	1.000508	0.928329	1.078299	0.989395
Direct Bilirubin	1.095907	0.932036	1.288589	0.267757
Indirect Bilirubin	1.03091	0.915937	1.160314	0.613865
K	0.97669	0.830217	1.149005	0.77602
Na	1.005811	0.980137	1.032159	0.660513
Cl	0.99758	0.913238	1.089713	0.957136
Mg	0.120206	0.003512	4.113869	0.239869
P	0.667578	0.209464	2.127617	0.494414
CRP	1.024328	1.007001	1.041952	0.005753
Ca	0.300189	0.047835	1.883842	0.199096
GFR	0.96458	0.941504	0.988221	0.003511
Amyloid	1.001978	1.000766	1.003192	0.001374
C1q	1.008992	0.996395	1.021747	0.162561
CK-MB	1.234022	0.930305	1.636894	0.144623
PT	1.081185	0.873797	1.337794	0.472522
APTT	1.059444	0.963819	1.164557	0.23153
TT	0.995323	0.788852	1.255834	0.968472
Fibrinogen	1.430012	1.025764	1.993573	0.034856
D-D	1.745173	0.788434	3.862884	0.169564
INR	116.4343	0.215575	62887.33	0.13835
PCT	1.43E+11	1334.315	1.53E+19	0.006474
Blood Lactate	1.436125	0.81993	2.515405	0.205621
PH	1.108846	0.84153	1.461076	0.46289
$PaCO_2$	0.960499	0.918259	1.004683	0.079025
PaO_2	0.972351	0.952754	0.992351	0.006952
Oxygen concentration	1.026528	1.000762	1.052959	0.043523

Continued

Oxygenation Index	0.991652	0.987728	0.995591	3.41E−05
Serum Troponin	0.566605	0.002456	130.7373	0.837862
Myoglobin	1.011143	1.002275	1.020089	0.013678
TCD3 (%)	0.993133	0.970569	1.016221	0.556758
TCD4 (%)	0.986364	0.947917	1.026371	0.498528
TCD8 (%)	0.957084	0.903873	1.013426	0.132844
IL2	0.957149	0.821552	1.115126	0.574176
IL4	0.831517	0.501285	1.379297	0.474885
IL6	1.021095	0.99971	1.042937	0.053222
IL10	1.183976	1.037356	1.351319	0.01229
TNF	1.212997	0.853367	1.724185	0.281837
IFN	0.985827	0.920521	1.055767	0.683149
CD3	0.997504	0.995598	0.999413	0.010416
CD4	0.994224	0.989734	0.998735	0.012134
CD8	0.992234	0.986427	0.998076	0.009246
CD19	0.992116	0.983001	1.001316	0.092823
CD15	0.998545	0.994025	1.003085	0.529286
BCD	1.014728	0.977778	1.053074	0.439789
NK	1.045479	0.985567	1.109034	0.139644
CD4 (%)	0.969968	0.911867	1.03177	0.33327
CD8 (%)	0.956199	0.889725	1.027638	0.223089
CD4+CD8 (%)	0.988063	0.873836	1.117222	0.848072
Middle or Inner Band	3.178571	1.398358	7.225127	0.005775
Morphology	1.154643	0.920286	1.448681	0.214134
Density	1.692402	0.860912	3.326964	0.127087
Homogeneousness	1.034294	0.433926	2.465312	0.939352
Margin	1.416667	0.442968	4.530676	0.557063
Consolidation	3.103175	1.398634	6.88507	0.005351
Bronchial Inflation	1.850291	0.858916	3.985927	0.116055
Bronchiectasis	3.818182	1.694264	8.604628	0.00123
Blood vessels penetrated the lesion	1.079365	0.495782	2.349881	0.847426
Distribution along the vascular bundle	0.678571	0.314129	1.465829	0.323749
Adjacent vascular widening	0.989583	0.46112	2.123691	0.978558
Septal Thickening	1.417202	0.65672	3.058319	0.374278
Fibrosis	1.457271	0.643938	3.297897	0.366163

Note. Contact1: The history of contact with confirmed patients; Contact2: The history of contact with epidemic area; Days1: The incubation period (days); Days2: Treatment delay (days); Days3: Course of the disease (days).

0.992, 95% CI: 0.988 - 0.996, $P < 0.001$), myoglobin (OR: 1.011, 95% CI: 1.002 - 1.020, $P = 0.014$), IL-10 (OR: 1.184, 95% CI: 1.037 - 1.351, $P = 0.012$), consolidation (OR: 3.103, 95% CI: 1.399 - 6.885, $P = 0.005$), and bronchiectasis (OR: 3.818, 95% CI: 1.694 - 8.605, $P = 0.001$).

3.5. To Construct A Clinical-Image Nomogram for the Prediction of Severe COVID-19.

All the variables with $P < 0.05$ were screened for multivariable logistic regression. Table 5 and Figure 1 show the variables selected for predicting severe COVID-19 were age (OR: 1.03, 95% CI: 0.99 - 1.07, $P = 0.1565011$), body temperature (OR: 2.28, 95% CI: 1.01 - 5.18, $P = 0.0480145$), Lymphocyte count (OR: 0.11, 95% CI:0.03 - 0.38, $P = 0.0006512$), ADA (OR: 1.27, 95% CI: 1.08 - 1.49, $P = 0.0037539$), PaO_2 (OR: 0.98, 95% CI: 0.95 - 0.99, $P = 0.0511345$), IL-10 (OR: 1.15, 95% CI: 0.99 - 1.34, $P = 0.063646$), bronchiectasis (OR: 5.25, 95% CI: 1.77 - 5.62, $P = 0.0028594$). The final equation is: Nomoscore = 34.663 + Age × 0.028 + Temperature × 0.826 + L × −2.250 + ADA × 0.239 + PaO_2 × −0.023 + IL-10 × 0.143 + Bronchiectasis × 1.659. The established nomogram demonstrates in Figure 2 that clinicians can quickly obtain Nomoscore of a newly confirmed patient based on this figure to determine the likelihood that the patient will develop severe COVID-19.

Table 5. Multivariate logistic regression results predicting severity of COVID-19.

Variable	Odds Ratio	95%CI	*p*-value
Age	1.03	[0.99;1.07]	0.156501
Temperature	2.28	[1.01;5.18]	0.048015
L	0.11	[0.03;0.38]	0.000651
ADA	1.27	[1.08;1.49]	0.003754
PaO_2	0.98	[0.95;0.99]	0.051135
IL-10	1.15	[0.99;1.34]	0.063646
Bronchiectasis	5.25	[1.77;5.62]	0.002859

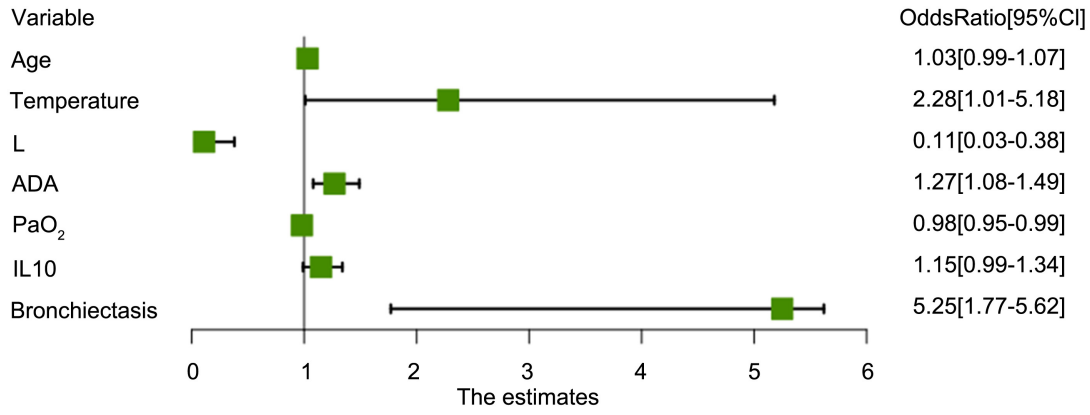

Figure 1. Multivariate logistic regression results predicting severity of COVID-19.

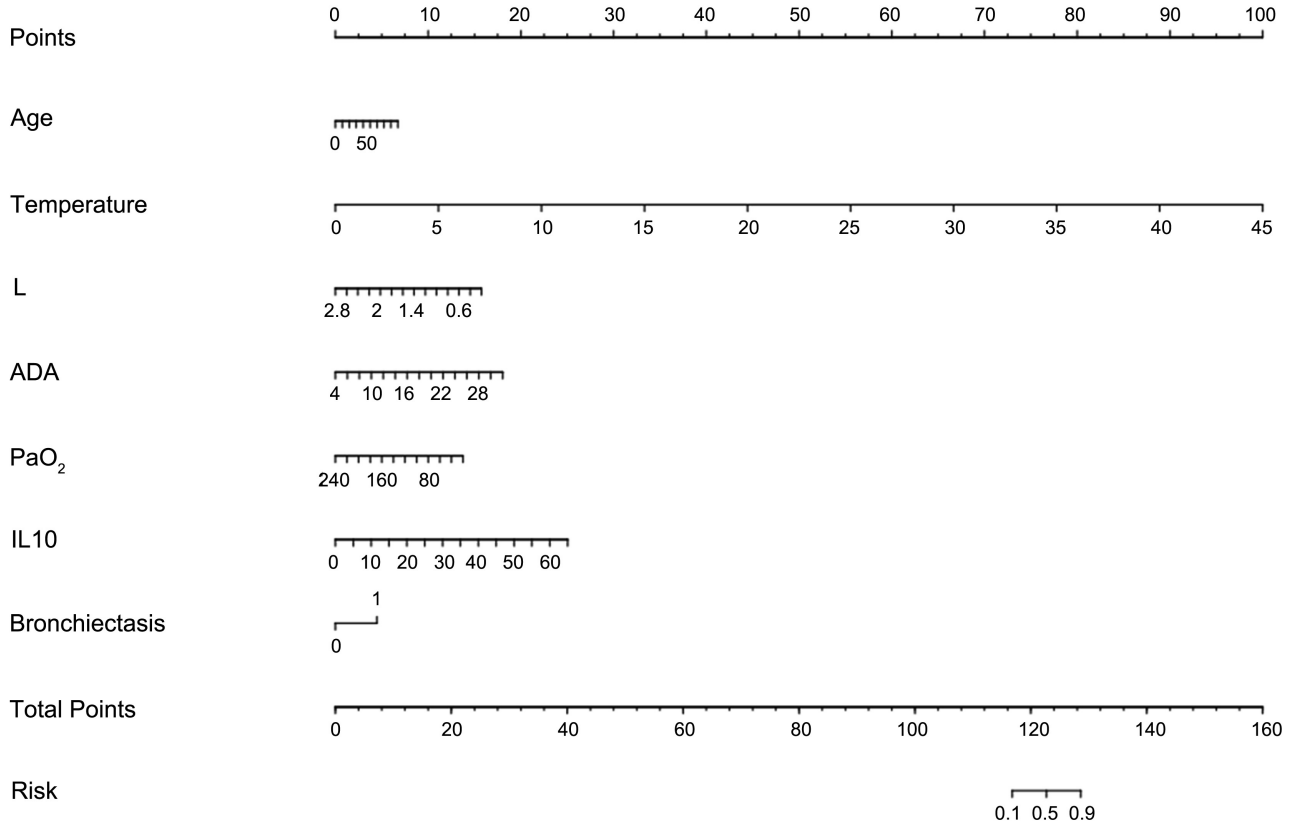

Figure 2. The nomogram for predicting severe COVID-19. According to the patient's age, body temperature, lymphocyte count, ADA value, PaO_2 value, IL-10 value, and whether bronchiectasis was present, the corresponding score was found by perpendicular to the first horizontal line. The probability of predicting severe COVID-19 is obtained by perpendicular the total score to the last horizontal line.

The constructed equation was used for drawing the ROC (**Figure 3**), with the area under the curve being 0.877. The Youden index was used for determining the optimal threshold, and the corresponding sensitivity and specificity were 74.29% and 82.73%, respectively.

4. Discussion

In this retrospective study, by analysing the medical history, clinical information, laboratory examination and CT images of COVID-19 patients who had cured and discharged from hospital, we found some factors related to the severity of the disease, such as age, body temperature, Lymphocyte count, ADA, PaO_2, IL-10, bronchiectasis, and established a stable nomogram. The nomogram established by us was highly sensitive and specific (74.29%, 82.73%). Clinicians could use this nomogram to predict the severity of COVID-19 patients newly diagnosed with a simple and feasible operation.

In the early stage of the COVID-19 outbreak, the severity of COVID-19 is judged mainly based on real-time clinical symptoms, laboratory examination, and imaging manifestations of the patient, which may lead to delayed treatments to some extent. Most of the patients in China have been cured and discharged

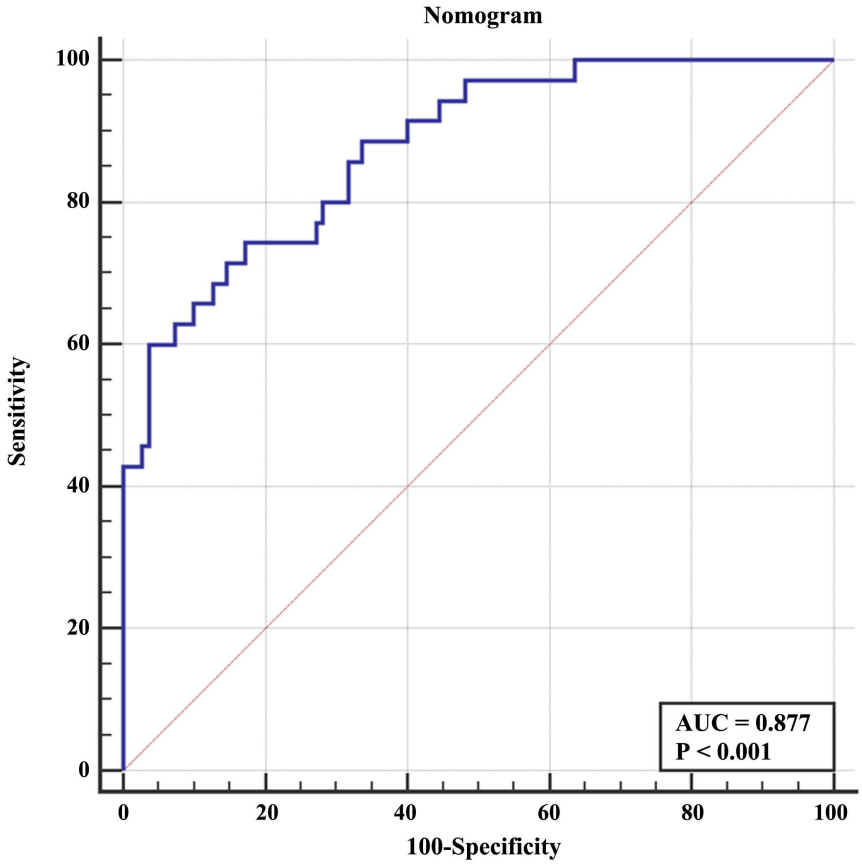

Figure 3. The receiver operating characteristic (ROC) curve of the nomogram predicting severe COVID-19.

from the hospital, so Chinese doctors have accumulated some experience for the diagnosis and treatment of COVID-19 [20] [21] [22] [23].

42% of the patients have been living in Wuhan for a long time or have been to Wuhan or had contact with people returning from Wuhan. This result was similar to that of other studies [24], which contact history was an important factor in the diagnosis of COVID-19. Our study also found that the average age of COVID-19 infected patients was 47.0 years (range, 4 - 86 years), which was similar to the findings of a previous study [20] [24]. The results of this study showed no statistical difference between men and women, but the study by Chen Nanshan *et al.* [25] found that the proportion of men was higher than that of women; hence, more data are needed for confirming the accuracy of this result. Most of the patients (62.3%) went to the hospital within 2 days of symptom onset. The average incubation period reported by Weijie Guan *et al.* was 4 days (2 - 7 days) [24], while that reported by Li Qun *et al.* was 5.2 days (4.1 - 7.0 days) [26]. Fever and cough were the most common clinical symptoms in all the cases, with fever occurring in 73.4% and cough in 63.6% of the patients. Compared with other studies, our results were different. In the study by Guan Weijie *et al.* [24], 43.8% of the patients were found to have fever at the first visit, but the number increased to 88.7% after hospitalisation. In our study, of all the patients with fever,

more than half had mild to moderate fever (37.5˚C - 39˚C), and only a few had a high fever (23.1%).

The laboratory test results of both the groups were abnormal to different degrees, especially in patients with severe diseases. Blood glucose, serum sodium, serum albumin, amyloid A, and CRP values were found to be outside the normal range in both the groups. We suggested that the difference in laboratory results between the 2 groups can be used for assessing the degree of illness to some extent. Sijiao Wang *et al.* suggested that older age, hypertension, diabetes, and lymphopenia were risk factors for severity of COVID-19 [22], which was somewhat similar with the result of our study. In addition, the possible explanation was that SARS-CoV-2, a novel virus, greatly triggers the body's innate immune response, adaptive response, and specific immune response after entering the body through the respiratory tract [27]. The specific immune response depends primarily on T cells, and the critical protective role of T cell immune response to coronavirus infection has been well documented in several animal models [28]. The virus can trigger a terrible cytokine storm in the pulmonary tissue by releasing various types of mediators causing edema, air exchange dysfunction and acute respiratory distress syndrome (ARDS), acute cardiac injury followed by secondary infection which may lead to death [29] [30] [31].

In the early stage of the disease or in non-severe patients, the body's innate immune response and specific response can prevent the spread and clearance of the virus, similar to the immune response to other viruses invading the body. The response includes increased blood glucose level, accelerated CRP rates, increased amyloid A level, and other adaptive responses, as well as diluent serum albumin and blood sodium reduction. With the progress of the disease, despite the efforts of T cells, CD4, CD8 and other lymphocytes were reduced in severe patients or in the later stage of the disease owing to the virulence of the virus or the decline of the body's immunity. Qin *et al.* reported that increased neutrophil-to-lymphocyte ratio (NLR) as well as T lymphopenia, especially decreased number of CD4+ T cells, was typical in COVID-19 patients, particularly among the severe cases; however, no significant alteration in the CD8+ cells and B cells was reported [32]. Whether the mechanism is similar to that of HIV causing CD4 cell depletion remains to be investigated [33] [34]. At the same time, if the treatment is working well or if the patient's immune system recovers, the multiple organ dysfunction gets reversed. However, if the disease continues to progress or the treatment measures are not effective, multiple organs will fail, especially the lung, resulting in death. In Dawei Wang's study of 138 inpatients in Wuhan, the mortality rate was 4.3% [27], while the mortality rate was 1.4% in another study [24]. Accurate death rates require further statistics.

In all the cases in this study, only one 18-year-old patient presented no obvious imaging manifestations at the time of admission, and all the others showed imaging changes. Among the remaining 138 cases assessed using imaging changes, the lesions were more localized in the lung periphery (98%), and only a few severe patients showed inner or middle band lesions. This result was similar to

that in the Wenzhou case imaging study [35]. Possible explanation was that the blood supply of the subpleural was less than that of the intrapulmonary and mediastinum band, with a reduction in lymphatic reflux, resulting in a relatively low virus clearance capacity. There were more patchy heterogeneous density shadows in the severe patients. The possible explanation was that different exudate protein content would lead to different density on CT imaging, resulting in a variety of shapes and density changes. In 60% of all the patients, the lesions were distributed along the lung texture, suggesting that the spread along the bronchi may be one of the mechanisms for the spread of the virus. In addition, CT signs such as consolidation, bronchial inflation, and bronchiectasis were more common in the severe group; therefore, these signs could be used for assessing the severity of the disease.

In this study, age, body temperature, lymphocyte count, ADA value, blood oxygen partial pressure, IL-10, and bronchiectasis signs were selected by statistical methods for predicting the severity of COVID-19 patients, and the role of each variable in the prediction of severe COVID-19 was directly demonstrated in the form of the nomogram. Other studies have found predictors that are similar to us, such as age and lymphocyte count, and different from us, such as chronic history [20] [22] [36]. Clinicians can predict the severity of newly admitted patients according to their age, laboratory examination, and CT performance, and grasp the trend of the patient's condition for conducting more active treatments. This will greatly facilitate the clinical treatment of COVID-19 and benefit potential severe COVID-19 patients.

This study has some limitations. First, this study is a retrospective study and not a random study, which may affect the integrity of the data and reduce the credibility of the results. Second, this study only collected cases in Taizhou city. It would be better to collect a larger range of cases and analyse larger data. Third, there was no long-term follow-up in this study, which could not strongly reflect the specific benefits brought to the patients by predicting the development of the disease. In the future, we will work as far as possible with hospitals in other regions to share each other's data, expand the amount of data in our research, and continuously improve our predictive models. In addition, we will conduct long-term follow-up visits to the patients studied to see how the severity of COVID-19 affects the patient's physical condition and quality of life later in life. If we have the conditions, we will conduct joint prospective studies in areas where new cases are occurring to verify the validity and stability of our model.

5. Conclusion

In summary, our study analyzed the cases of patients with COVID-19 in Taizhou city and constructed a model to predict the illness severity which was of great significance for early identification and prompt treatment. When patients showed the features including older age, high body temperature, low lymphocyte count, low ADA value, low PaO_2, high IL-10, and bronchiectasis sign predict a greater likelihood of severe COVID-19.

Declarations

Ethics Approval and Consent to Participate

The retrospective multicentre cohort study was approved by the ethics review committee of Taizhou Hospital, Sanmen People's Hospital, Wenling First People's Hospital, and Tiantai People's Hospital, and the written informed consent was waived.

Consent for Publication

All authors agreed to publish the manuscript in the journal of International Journal of Clinical Medicine.

Availability of Data and Materials

All datasets are presented in the main paper.

Authors' Contributions

YK, SH and WJ designed the study and took the lead in drafting the manuscript and interpreting, SL and PP developed the statistical methods, SH, RZ, JW, RZZ, RL, HL, ZZ were participated in the collection of experimental data. All authors read and approved the final manuscript for publication.

Acknowledgements

We thank Jingjing Li and Shuying Ying for their contribution to date collection for this study. We would also like to thank Editage (www.editage.cn) for English language editing.

Conflicts of Interest

The authors declare that they have no competing interests.

References

[1] Wang, W., Tang, J. and Wei, F. (2020) Updated Understanding of the Outbreak of 2019 Novel Coronavirus (2019-nCoV) in Wuhan, China. *Journal of Medical Virology*, **92**, 441-447. http://www.ncbi.nlm.nih.gov/pubmed/31994742 https://doi.org/10.1002/jmv.25689

[2] Hui, D.S., Azhar, I.E., Madani, T.A., Ntoumi, F., Kock, R., Dar, O., *et al.* (2020) The Continuing 2019-nCoV Epidemic Threat of Novel Coronaviruses to Global Health: The Latest 2019 Novel Coronavirus Outbreak in Wuhan, China. *International Journal of Infectious Diseases*, **91**, 264-266. https://doi.org/10.1016/j.ijid.2020.01.009

[3] Bassetti, M., Vena, A. and Roberto, G.D. (2020) The Novel Chinese Coronavirus (2019-nCoV) Infections: Challenges for Fighting the Storm. *European Journal of Clinical Investigation*, **50**, e13209. https://doi.org/10.1111/eci.13209

[4] Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., *et al.* (2020) Genomic Characterisation and Epidemiology of 2019 Novel Coronavirus: Implications for Virus Origins and Receptor Binding. *The Lancet*, **395**, 565-574. https://doi.org/10.1016/S0140-6736(20)30251-8

[5] Rothe, C., Schunk, M., Sothmann, P., Bretzel, G., Froeschl, G., Wallrauch, C., *et al.* (2020) Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. *New England Journal of Medicine*, **382**, 970-971. https://doi.org/10.1056/NEJMc2001468

[6] Phan, L.T., Nguyen, T.V., Luong, Q.C., Nguyen, T.V., Nguyen, H.T., Le, H.Q., *et al.* (2020) Importation and Human-to-Human Transmission of a Novel Coronavirus in Vietnam. *New England Journal of Medicine*, **382**, 872-874. https://doi.org/10.1056/NEJMc2001272

[7] Chan, J.F.W., Yuan, S., Kok, K.H., To, K.K.W., Chu, H., Yang, J., *et al.* (2020) A Familial Cluster of Pneumonia Associated with the 2019 Novel Coronavirus Indicating Person-to-Person Transmission: A Study of a Family Cluster. *The Lancet*, **395**, 514-523. https://doi.org/10.1016/S0140-6736(20)30154-9

[8] Wu, J.T., Leung, K. and Leung, G.M. (2020) Nowcasting and Forecasting the Potential Domestic and International Spread of the 2019-nCoV Outbreak Originating in Wuhan, China: A Modelling Study. *The Lancet*, **395**, 689-697. https://doi.org/10.1016/S0140-6736(20)30260-9

[9] China D. Dingxiang Garden, Doctor Dingxiang, Real-Time Status of New Coronavirus Pneumonia. 5. https://ncov.dxy.cn/ncovh5/view/pneumonia?from=singlemessage&isappinstalled=0

[10] Ren, W., Qu, X., Li, W., Han, Z., Yu, M., Zhou, P., *et al.* (2008) Difference in Receptor Usage between Severe Acute Respiratory Syndrome (SARS) Coronavirus and SARS-Like Coronavirus of Bat Origin. *Journal of Virology*, **82**, 1899-1907. http://jvi.asm.org/content/82/4/1899.abstract https://doi.org/10.1128/JVI.01085-07

[11] Maier, H.J., Bickerton, E. and Britton, P. (2015) Coronaviruses: An Overview of Their Replication and Pathogenesis. *Coronaviruses—Methods and Protocols*, **1282**, 1-23. https://doi.org/10.1007/978-1-4939-2438-7

[12] Hemida, M.G., Elmoslemany, A., Al-hizab, F., Alnaeem, A., Almathen, F., Faye, B., *et al.* (2018) Dromedary Camels and the Transmission of Middle East Respiratory Syndrome Coronavirus (MERS-CoV). *Transboundary and Emerging Diseases*, **64**, 344-353. https://doi.org/10.1111/tbed.12401

[13] Kucharski, A.J. and Althaus, C.L. (2015) The Role of Superspreading in Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Transmission. *Eurosurveillance*, **20**, 14-18. https://doi.org/10.2807/1560-7917.ES2015.20.25.21167

[14] Mackay, I.M. and Arden, K.E. (2015) MERS Coronavirus: Diagnostics, Epidemiology and Transmission. *Virology Journal*, **12**, Article No. 222. https://doi.org/10.1186/s12985-015-0439-5

[15] Azhar, E.I., Hui, D.S.C., Memish, Z.A., Drosten, C. and Zumla, A. (2019) The Middle East Respiratory Syndrome (MERS). *Infectious Disease Clinics of North America*, **33**, 891-905. https://doi.org/10.1016/j.idc.2019.08.001

[16] Lim, J., Jeon, S., Shin, H.Y., Kim, M.J., Seong, Y.M., Lee, W.J., *et al.* (2020) Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: The Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR. *Journal of Korean Medical Science*, **35**, e79. https://pubmed.ncbi.nlm.nih.gov/32056407 https://doi.org/10.3346/jkms.2020.35.e89

[17] COVID-19 National Incident Room Surveillance Team (2020) COVID-19, Australia: Epidemiology Report 2 (Reporting Week Ending 19:00 AEDT 8 February 2020). *Communicable Diseases Intelligence*, **12**, 44.

https://pubmed.ncbi.nlm.nih.gov/32050080
https://doi.org/10.33321/cdi.2020.44.14

[18] Status, C., Ahn, D., Shin, H., Kim, M., Lee, S., Kim, H., *et al.* (2020) Current Status of Epidemiology, Diagnosis, Therapeutics, and Vaccines for Novel Coronavirus Disease 2019 (COVID-19). *Journal of Microbiolog and Biotechnology*, **30**, 313-324. https://doi.org/10.4014/jmb.2003.03011

[19] New Coronavirus Diagnosis and Treatment Protocol (Trial Version 5). *Chinese Journal of Integrated Traditional and Western Medicine*, 1-3. http://kns.cnki.net/kcms/detail/11.2787.R.20200208.1034.002.htm

[20] Zhang, S.Y., Lian, J.S., Hu, J.H., Zhang, X.L., Lu, Y.F., Cai, H., *et al.* (2020) Clinical Characteristics of Different Subtypes and Risk Factors for the Severity of Illness in Patients with COVID-19 in Zhejiang, China. *Infectious Diseases of Poverty*, **9**, Article No. 85. https://doi.org/10.1186/s40249-020-00710-6

[21] Lian, J., Jin, X., Hao, S., Jia, H., Cai, H., Zhang, X., *et al.* (2020) Epidemiological, Clinical, and Virological Characteristics of 465 Hospitalized Cases of Coronavirus Disease 2019 (COVID-19) from Zhejiang Province in China. *Influenza and Other Respiratory Viruses*, **14**, 564-574. https://doi.org/10.1111/irv.12758

[22] Wang, S., Chen, Z., Lin, Y., Lin, L., Lin, Q., Fang, S., *et al.* (2020) Clinical Characteristics of 199 Discharged Patients with COVID-19 in Fujian Province: A Multicenter Retrospective Study between January 22nd and February 27th, 2020. *PLoS ONE*, **15**, e0242307. https://doi.org/10.1371/journal.pone.0242307

[23] Jin, X., Lian, J.S., Hu, J.H., Gao, J., Zheng, L., Zhang, Y.M., *et al.* (2020) Epidemiological, Clinical and Virological Characteristics of 74 Cases of Coronavirus-Infected Disease 2019 (COVID-19) with Gastrointestinal Symptoms. *Gut*, **69**, 1002-1009. https://doi.org/10.1136/gutjnl-2020-320926

[24] Guan, W.-J., Ni, Z.-Y., Hu, Y., Liang, W.-H., Ou, C.-Q., He, J.-X., *et al.* (2020) Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine*, **382**, 1708-1720. https://doi.org/10.1056/NEJMoa2002032

[25] Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., *et al.* (2020) Epidemiological and Clinical Characteristics of 99 Cases of 2019 Novel Coronavirus Pneumonia in Wuhan, China: A Descriptive Study. *The Lancet*, **395**, 507-513. https://doi.org/10.1016/S0140-6736(20)30211-7

[26] Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., *et al.* (2020) Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *New England Journal of Medicine*, 1-9.

[27] Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., *et al.* (2020) Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*, **323**, 1061-1069. https://doi.org/10.1001/jama.2020.1585

[28] Liu, W.J., Zhao, M., Liu, K., Xu, K., Wong, G., Tan, W., *et al.* (2017) T-Cell Immunity of SARS-CoV: Implications for Vaccine Development against MERS-CoV. *Antiviral Research*, **137**, 82-92. https://doi.org/10.1016/j.antiviral.2016.11.006

[29] Saghazadeh, A. and Rezaei, N. (2020) Immune-Epidemiological Parameters of the Novel Coronavirus—A Perspective. *Expert Review of Clinical Immunology*, **16**, 465-470. https://doi.org/10.1080/1744666X.2020.1750954

[30] Pinsky, M.R. (2004) Dysregulation of the Immune Response in Severe Sepsis. *The American Journal of the Medical Sciences*, **328**, 220-229. https://doi.org/10.1097/00000441-200410000-00005

[31] Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., *et al.* (2020) Clinical Features

of Patients Infected with 2019 Novel Coronavirus in Wuhan, China. *The Lancet*, **395**, 497-506.

[32] Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y., *et al.* (2020) Dysregulation of Immune Response in Patients with COVID-19 in Wuhan, China. *SSRN Electronic Journal*. https://doi.org/10.2139/ssrn.3541136

[33] Agosto, L.M. and Henderson, A.J. (2018) CD4+ T Cell Subsets and Pathways to HIV Latency. *AIDS Research and Human Retroviruses*, **34**, 780-789. https://doi.org/10.1089/aid.2018.0105

[34] Akiyama, H., Miller, C.M., Ettinger, C.R., Belkina, A.C., Snyder-Cappione, J.E. and Gummuluru, S. (2018) HIV-1 Intron-Containing RNA Expression Induces Innate Immune Activation and T Cell Dysfunction. *Nature Communications*, **9**, 3450. https://doi.org/10.1038/s41467-018-05899-7

[35] Yang, W., Cao, Q., Qin, L., Wang, X., Cheng, Z., Pan, A., *et al.* (2020) Clinical Characteristics and Imaging Manifestations of the 2019 Novel Coronavirus Disease (COVID-19): A Multi-Center Study in Wenzhou City, Zhejiang, China. *Journal of Infection*, **80**, 388-393. https://doi.org/10.1016/j.jinf.2020.02.016

[36] Wang, F., Qu, M., Zhou, X., Zhao, K., Lai, C., Tang, Q., *et al.* (2020) The Timeline and Risk Factors of Clinical Progression of COVID-19 in Shenzhen, China. *Journal of Translational Medicine*, **18**, Article No. 270. https://doi.org/10.1186/s12967-020-02423-8

List of Abbreviations

CT: Computed tomography;
WHO: World Health Organization;
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2;
SARS-CoV: Severe acute respiratory syndrome coronavirus;
MERS-CoV: Middle east respiratory syndrome coronavirus;
PHEIC: Public Health Emergency of International Concern;
COVID-19: Coronavirus disease 2019;
CDC: Center for Disease Control and Prevention;
RT-PCR: reverse transcription polymerase chain reaction;
NGS: high throughput sequencing;
$PaCO_2$: Arterial blood oxygen partial pressure;
RR: Respiratory Rate;
FiO_2: oxygen concentration;
PH: potential of hydrogen;
C1q: Human Complement Component C1q;
IL-10: Interleukin-10;
TCD3: Total cluster of differentiation 3;
PT: Prothrombin time;
ADA: adenosine deaminase;
CK: Creatinine kinase;
LDH: Lactate dehydrogenase;
CRP: C-reactive protein;
HIV: Human immunodeficiency virus;
CD3/4/8: cluster of differentiation 3/4/8.