Clinical Characteristics, Risk Factors and Predictive Value of COVID-19 Pneumonia: A Retrospective Study of 173 Patients in Wuhan, China

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Research Article

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Abstract

Background: COVID-19 is a globally emerging infectious disease. As the global epidemic continues to spread, the risk of COVID-19 transmission and diffusion in the world will also remain. Currently, several studies describing its clinical characteristics have focused on the initial outbreak, but rarely to the later stage. Here we described clinical characteristics, risk factors for disease severity and in-hospital outcome in patients with COVID-19 pneumonia from Wuhan.

Methods: Patients with COVID-19 pneumonia admitted to Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology from February 13 to March 8, 2020, were retrospectively enrolled. Multivariable logistic regression analysis was used to identify risk factors for disease severity and in-hospital outcome and establish predictive models. Receiver operating characteristic (ROC) curve was used to assess the predictive value of above models.

Results: 106 (61.3%) of the patients were female. The mean age of study populations was 62.0 years, of whom 73 (42.2%) had underlying comorbidities mainly including hypertension (24.9%). The most common symptoms on admission were fever (67.6%) and cough (60.1%), digestive symptoms (22.0%) was also very common. Older age (OR: 3.420; 95%CI: 1.415-8.266; P=0.006), diarrhea (OR: 0.143; 95%CI: 0.033-0.611; P=0.009) and lymphopenia (OR: 4.769; 95%CI: 2.019-11.266; P=0.000) were associated with severe illness on admission; the area under the ROC curve (AUC) of predictive model were 0.860 (95%CI: 0.802-0.918; P=0.000). Older age (OR: 0.309; 95%CI: 0.142-0.674; P=0.003), leucopenia (OR: 0.165; 95%CI: 0.034-0.793; P=0.025), increased lactic dehydrogenase (OR: 0.257; 95%CI: 0.100-0.659; P=0.005) and interleukins-6 levels (OR: 0.294; 95%CI: 0.099-0.872; P=0.027) were associated with poor in-hospital outcome; AUC of predictive model were 0.752 (95%CI: 0.681-0.824; P=0.000).

Conclusion: Older patients with diarrhea and lymphopenia need early identification and timely intervention to prevent the progression to severe COVID-19 pneumonia. However, older patients with leucopenia, increased lactic dehydrogenase and interleukins-6 levels are at a high risk for poor in-hospital outcome.

Trial registration: ChiCTR2000029549

Background

Coronavirus disease 2019 (COVID-19) is an infection caused by a novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) [1]. Coronaviruses can infect a wide range of hosts including humans, mainly leading to respiratory infections, such as SARS and Middle East respiratory syndrome (MERS) [2]. Most COVID-19 patients have a good prognosis, but few patients become severe illness or even die, mainly due to inflammatory storm caused by hyperimmune function [3]. As of June 4, 2020, COVID-19 has affected more than 6 million confirmed cases in 216 countries and territories, including about 380,000 deaths [4–5].

Currently, several studies describing clinical characteristics of COVID-19 pneumonia in Wuhan have focused on the initial outbreak [6–8], but rarely to the later stage. Similar to SARS, COVID-19 pneumonia may have different epidemiological and clinical characteristics at various stages [9]. Here we described clinical

characteristic and risk factors of confirmed cases who were admitted to the Cancer Center of Wuhan Union Hospital from February 13 to March 8, 2020.

Methods

Study design

In this retrospective single-center study, we described clinical characteristics of patients with COVID-19 pneumonia admitted to Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology from February 13 to March 8, 2020, and analyzed risk factors for disease severity and in-hospital outcome.

Diagnosis and clinical types

According to WHO interim guidance and the diagnostic and treatment guidelines issued by the Chinese National Health Committee (version 5), COVID-19 pneumonia were mainly confirmed by chest computed tomography (CT) and SARS-CoV-2 nucleic acids test in throat swab [10–11].

As suggested, COVID-19 pneumonia was divided into four types. Mild type had minimal clinical symptoms and no imaging findings of pneumonia. Common type had fever, respiratory and other symptoms, and imaging findings of pneumonia. Severe type met any of the following: (1) respiratory distress with respiratory frequency ≥ 30 times/minutes; (2) pulse oximeter oxygen saturation at rest ≤ 93%; (3) arterial oxygen partial pressure (PaO_2) /inspired oxygen fraction (FiO_2) ratio ≤ 300 mm Hg (1 mmHg = 0.133 kPa). Critically severe type met any of the following: (1) respiratory failure requiring mechanical ventilation; (2) shock; (3) combination with other organ failure requiring monitoring and treatment of intensive care unit [10–11]. Here we combined into severe illness (mild/common type) and non-severe illness (severe/critically severe type).

Discharge criteria

According to China guidelines, the discharge standards for patients with COVID-19 pneumonia met all of the following: (1) body temperature returned to normal for more than 3 days; (2) respiratory symptoms improved significantly; (3) lung imaging showed obvious absorption of inflammation; (4) two consecutive nucleic acid test for respiratory pathogens was negative (the sampling interval is at least one day) [11].

Data extraction

We collected relevant data from electronic medical records, including epidemiologic and demographic information, comorbidities, symptoms, laboratory and CT findings, treatment, as well as in-hospital outcome (discharge, hospitalization/death) on March 8, 2020. Serum cytokine levels such as interleukins (IL)-2, IL-4, IL-6, IL-10, tumor necrosis factor-a, and interferon-γ, were measured on admission. The data of each patient was carefully examined by at least two researchers and then entered into a computer database.

Statistical analysis

Continuous variables were described by median and interquartile range (IQR), while categorical variables were expressed as the counts and percentages. Univariate analysis (Chi-square tests or Fisher's exact tests) and multivariable logistic regression analysis were used to identify risk factors for disease severity and in-hospital outcome, and establish predictive models. Further, receiver operating characteristic (ROC) curve was drawn and the area under the ROC curve (AUC) was calculated to assess the predictive value of above models. All tests were 2-tailed, and the level of significance was P = 0.05. Statistical tests were performed using SPSS version 22.0 software.

Results

Clinical characteristics

Clinical characteristics are shown in Table 1. From February 13 to March 8, 2020, a total of 173 patients with COVID-19 pneumonia were admitted to the Cancer Center of Wuhan Union Hospital and enrolled in the study. Among them, 67 (38.7%) were male while 106 (61.3%) were female. The patients ranged in age from 18 to 96 years, with the median age of 62 years (IQR 49–69 years), of whom 64 (37.0%) were over 65 years of age. 42.2% of patients had underlying comorbidities, the more common of which were diabetes mellitus (17/173, 9.8%), hypertension (43/173, 24.9%) and heart disease (15/173, 8.7%). Intriguingly, this study did not find any congenital or acquired immunodeficiency in these patients.

The median time from onset to admission was 15 days (IQR 7–22 days), and 45.7% of patients were admitted within 12 days after onset. The symptoms on admission in the order of frequency were: fever (117/173, 67.6%), cough (104/173, 60.1%), dyspnea (56/173, 32.4%), fatigue (52/173, 30.1%), oppression in chest (43/173, 24.9%), muscular soreness (29/173, 16.8%), diarrhea (23/173, 13.3%), expectoration (18/173, 10.4%), sore throat (14/173, 8.1%), anorexia (10/173, 5.8%), chilly (9/173, 5.2%), nausea (7/173, 4.0%), headache (6/173, 3.5%), vomiting (6/173, 3.5%), nasal obstruction (2/173, 1.2%), and abdominal pain (2/173, 1.2%).

During hospitalization, totally 166 patients (96.0%) received antiviral treatment, and 77 patients (44.5%) received antibiotic treatment. The antiviral drugs are mainly abiolol (164/173, 94.8%), but also recombinant Human Interferon α-2b (7/173, 4.0%), oseltamivir (30/173, 17.3%), ribavirin (8/173, 4.6%), ganciclovir (2/173, 1.2%), and hydroxychloroquine (2/173, 1.2%).

Table 1
Clinical characteristics of 173 patients with COVID-19 pneumonia.

Characteristics	All patients (n = 173)	Severe illness (n =67)	Not severe illness (n =106)	p	Discharged (n = 90)	Not discharged (n = 83)	P
Male	67(38.7%)	30(44.8%)	37(34.9%)	0.194	36(40%)	31(37.3%)	0.721
Age > 65 years	64(37.0%)	37(55.2%)	27(25.5%)	0.000	23(25.6%)	41(49.4%)	0.001
Time from onset to admission ≤ 12 days	79(45.7%)	40(59.7%)	39(36.8%)	0.003	43(47.8%)	36(43.4%)	0.561
Comorbidities							
Diabetes mellitus	17(9.8%)	9(13.4%)	8(7.5%)	0.205	5(5.6%)	12(14.5%)	0.049
Hypertension	43(24.9%)	23(34.3%)	20(18.9%)	0.022	20(22.2%)	23(27.7%)	0.404
Heart disease	15(8.7%)	11(16.4%)	4(3.8%)	0.010	5(5.6%)	10(12.0%)	0.129
Stroke	4(2.3%)	4(6%)	0	0.043	2(2.2%)	2(2.4%)	1.000
Cancer	5(2.9%)	3(4.5%)	2(1.9%)	0.600	2(2.2%)	3(3.6%)	0.927
Symptoms							
Fever	117(67.6%)	49(73.1%)	68(64.2%)	0.219	60(66.7%)	57(68.7%)	0.778
Cough	104(60.1%)	42(62.7%)	62(58.5%)	0.583	53(58.9%)	51(61.4%)	0.732
Expectoration	18(10.4%)	6(9.0%)	12(11.3%)	0.620	10(11.1%)	8(9.6%)	0.751
Fatigue	52(30.1%)	22(32.8%)	30(28.3%)	0.526	26(28.9%)	26(31.3%)	0.727
Sore throat	14(8.1%)	0	14(13.2%)	0.002	8(8.9%)	6(7.2%)	0.689
Headache	6(3.5%)	2(3.0%)	4(3.8%)	1.000	4(4.4%)	2(2.4%)	0.753
Chilly	9(5.2%)	1(1.5%)	8(7.5%)	0.163	5(5.6%)	4(4.8%)	1.000
Nasal obstruction	2(1.2%)	0	2(1.9%)	0.523	2(2.2%)	0	0.498
Dyspnea	56(32.4%)	22(32.8%)	34(32.1%)	0.917	30(33.3%)	26(31.3%)	0.778
Oppression in chest	43(24.9%)	16(23.9%)	27(25.5%)	0.313	24(26.7%)	19(22.9%)	0.566
Muscular soreness	29(16.8%)	8(11.9%)	21(19.8%)	0.177	17(18.9%)	12(14.5%)	0.436
Diarrhea	23(13.3%)	4(6.0%)	19(17.9%)	0.024	12(13.3%)	11(13.3%)	0.988
Abdominal pain	2(1.2%)	0	2(1.9%)	0.523	0	2(2.4%)	0.229

Characteristics	All patients (n = 173)	Severe illness (n =67)	Not severe illness (n =106)	p	Discharged (n = 90)	Not discharged (n = 83)	P
Nausea	7(4.0%)	4(6.0%)	3(2.8%)	0.532	2(2.2%)	5(6.0%)	0.378
Vomiting	6(3.5%)	4(6.0%)	2(1.9%)	0.316	2(2.2%)	4(4.8%)	0.605
Anorexia	10(5.8%)	6(9.0%)	4(3.8%)	0.276	4(4.4%)	6(7.2%)	0.647
Treatment							
Antiviral drugs	166(96.0%)	63(94.0%)	103(97.2%)	0.532	85(94.4%)	81(97.6%)	0.507
Antibiotics	77(44.5%)	23(34.3%)	54(50.9%)	0.032	37(41.1%)	40(48.2%)	0.349

Laboratory findings

Laboratory findings are shown in Table 2. Lymphopenia (69/173, 39.9%), leucopenia (14/173, 8.1%), neutropenia (13/173, 7.5%), anemia (56/173, 32.4%) and thrombocytosis (15/173, 8.7%) were common abnormal results of blood routine in patients with COVID-19 pneumonia. In addition to severe lung damage, COVID-19 pneumonia also caused multiple organs such as liver, heart, kidneys, manifested by increased alanine aminotransferase (35/173, 20.2%), aspartate transaminase (32/173, 18.5%), lactic dehydrogenase (LDH) (34/173, 19.7%), creatine kinase (18/173, 10.4%) and creatinine (1/173, 0.6%). Further, many patients had abnormal levels of serum cytokines, especially interleukins. The incidences of increased IL-2, IL-4, IL-6 and IL-10 levels were 8.7% (15/173), 95.4% (165/173), 17.9% (31/173), and 21.4% (37/173), respectively.

Table 2
Laboratory findings of 173 patients with COVID-19 pneumonia.

Characteristics	All patients (n = 173)	Severe illness (n =67)	Not severe illness (n =106)	p	Discharged (n = 90)	Not discharged (n = 83)	P
White blood cell count							
< 3.5 × 10^9/L	14(8.1%)	8(11.9%)	6(5.7%)	0.140	3(3.3%)	11(13.3%)	0.017
> 9.5 × 10^9/L	6(3.5%)	5(7.5%)	1(0.9%)	0.063	2(2.2%)	4(4.8%)	0.605
Neutrophil count							
< 1.8 × 10^9/L	13(7.5%)	7(10.4%)	6(5.7%)	0.245	5(5.6)	8(9.6%)	0.309
> 6.3 × 10^9/L	9(5.2%)	8(11.9%)	1(0.9%)	0.005	4(4.4%)	5(6.0%)	0.901
Lymphocyte count < 1.1 × 10^9/L	69(39.9%)	44(65.7%)	25(23.6%)	0.000	29(32.2%)	40(48.2%)	0.032
Platelet count							
< 125 × 10^9/L	12(6.9%)	7(10.4%)	5(4.7%)	0.255	5(5.6%)	7(8.4%)	0.457
> 350 × 10^9/L	15(8.7%)	6(9.0%)	9(8.5%)	0.916	8(8.9%)	7(8.4%)	0.915
Hemoglobin							
< 115 g/L	56(32.4%)	26(38.8%)	30(28.3%)	0.150	21(23.3%)	35(42.2%)	0.008
> 150 g/L	9(5.2%)	4(6.0%)	5(4.7%)	0.992	6(6.7%)	3(3.6%)	0.575
Creatinine > 133 μmol/L	1(0.6%)	1(1.5%)	0	0.387	1(1.1%)	0	1.000
Aspartate transaminase > 40 U/L	32(18.5%)	18(26.9%)	14(13.2%)	0.024	12(13.3%)	20(24.1%)	0.069
Alanine aminotransferase > 40 U/L	35(20.2%)	14(20.9%)	21(19.8%)	0.863	19(21.1%)	16(19.3%)	0.764
Lactic dehydrogenase > 245 U/L	34(19.7%)	21(31.3%)	13(12.3%)	0.002	9(10%)	25(30.1%)	0.001
Creatine kinase > 174 U/L	18(10.4%)	12(17.9%)	6(5.7%)	0.010	11(12.2%)	7(8.4%)	0.415
Interleukins-2 > 4.1 ng/L	15(8.7%)	5(7.5%)	10(9.4%)	0.654	5(5.6%)	10(12.0%)	0.129
Interleukins-4 > 3.2 ng/L	165(95.4%)	66(98.1%)	99(93.4%)	0.235	84(93.3%)	81(97.6%)	0.332

Characteristics	All patients (n = 173)	Severe illness (n =67)	Not severe illness (n =106)	p	Discharged (n = 90)	Not discharged (n = 83)	P
Interleukins-6 > 2.9 ng/L	31(17.9%)	9(13.4%)	22(20.8%)	0.221	10(11.1%)	21(25.3%)	0.015
Interleukins-10 > 5.0 ng/L	37(21.4%)	21(31.3%)	16(15.1%)	0.011	13(14.4%)	24(28.9%)	0.020
Tumor necrosis factor-a > 23.0 ng/L	3(1.7%)	3(4.5%)	0	0.110	1(1.1%)	2(2.4%)	0.944
Interferon-γ > 18.0 ng/L	2(1.2%)	1(1.5%)	1(0.9%)	1.000	1(1.1%)	1(1.2%)	1.000

Risk factors for disease severity and their predictive value

On admission, there were 106 non-severe patients (61.3%) and 67 severe patients (38.7%). Univariate analysis showed that age > 65 years, time from onset to admission ≤ 12 days, presence of comorbidities (hypertension, heart disease and stroke), sore throat, diarrhea, neutrophilia, lymphopenia, increased LDH, aspartate transaminase, creatine kinase and IL-10 levels were associated with disease severity ($P < 0.05$). On multivariate analysis, age > 65 years, diarrhea and lymphopenia were found to be independent risk factors of severe illness ($P < 0.05$). In ROC curve analysis, AUC of predictive model based on above indicators were 0.860 (95%CI: 0.802–0.918; $P = 0.000$), with a sensitivity of 74.6% and a specificity of 84.0% (Fig. 1).

Risk factors for in-hospital outcome and their predictive value

As of March 8, 2020, 90 patients (52.0%) were discharged, and 83 patients (48.0%) were not discharged (2 deaths). For discharged and undischarged patients, the median time from onset to admission were 14 days (IQR 7–20 days) and 15 days (IQR 7–24 days), and the median time for hospitalization were 11 days (IQR 9–17 days) and 21 days (IQR 12–22 days). Two patients died on the 7th and 9th days after admission, respectively.

On univariate analysis, age > 65 years, presence of comorbidities (diabetes mellitus), leucopenia, lymphopenia, anemia, increased LDH, IL-6 and IL-10 levels were associated with in-hospital outcome ($P < 0.05$). Multivariate analysis showed that age > 65 years, leucopenia, increased LDH and IL-6 levels were associated with poor in-hospital outcome ($P < 0.05$). In ROC curve analysis, AUC of above predictive model were 0.752 (95%CI: 0.681–0.824; $P = 0.000$), with a sensitivity of 55.6% and a specificity of 83.1% (Fig. 2).

Table 3
Multivariate logistic regression analysis of risk factors for 173 patients with COVID-19 pneumonia.

Risk factors	Odd ratios	95%CI	P
For severe illness			
Age > 65 years	3.420	1.415–8.266	0.006
Diarrhea	0.143	0.033–0.611	0.009
Lymphopenia	4.769	2.019–11.266	0.000
For poor in-hospital outcome			
Age > 65 years	0.309	0.142–0.674	0.003
Leucopenia	0.165	0.034–0.793	0.025
Increased lactic dehydrogenase level	0.257	0.100-0.659	0.005
Increased interleukins − 6 level	0.294	0.099–0.872	0.027

Discussion

In this study, 67 (38.7%) of the patients were males, and the severe illness rate was 44.8% in males but 34.9% in females. Sex differences have been reported regarding the susceptibility, severity and outcome of COVID-19 pneumonia. In addition to estrogen protection and different lifestyle, angiotensin-converting enzyme (ACE) 2 may explain sex differences. ACE2 is a receptor for SARS-CoV-2 entry into cells, and its higher expression in male lungs may correlate with high prevalence, severe illness rate and mortality in males [12–14]. However, our data did not confirm sex differences in COVID-19 pneumonia. This may result from different study periods and trial designs.

The median age of our cases [62.0 years (IQR 49–69)] was much higher than that reported by Chen [15] and Zhang [16], potentially leading to more comorbidities. Similar to other recent reports [17–18], the most common comorbidities were hypertension (24.9%), diabetes mellitus (9.8%) and heart disease (8.7%). Cumulative studies confirmed that older age and comorbidities were associated with severe COVID-19 pneumonia and poor outcomes [6, 8, 19]. Also, our data supported older age as a risk factor. In the process of developing severe illness, inflammatory storm usually plays an important role. Comprehensive genomic analyses exhibited that older animals had stronger host innate immune response to SARS-CoV infection, and tended to develop more severe pneumonia [20].

Although the main symptoms were fever and respiratory symptoms, digestive symptoms were also very common. In our report, almost a quarter of patients (22.0%) had digestive symptoms, consistent with that reported by Dan [21], but much higher than that reported by Guan [6]. Previous univariate analysis showed that the patients with digestive symptoms were at greater risk of severe illness of COVID-19 pneumonia [22–23]. On multivariate logistic regression analysis, we further found that diarrhea was associated with patients with severe illness. After cells in lungs are infected by SARS-CoV-2, effector CD4 + T cells migrate to the small intestine through the gut-lung axis, thereby causing intestinal flora imbalance and diarrhea. In turn, abnormal

intestinal flora fails to regulate the host's immune response, leading to inflammation storm closely associated with lungs and vital organ systems [24–25].

The lymphocytes counts serves as a reference indicator in the diagnosis of COVID-19 pneumonia [11]. In this study, peripheral blood lymphocytes counts were even lower in severe illness than in non-severe illness, possibly due to the recruitment of lymphocytes from the peripheral blood to lungs by the SARS-CoV-2 [26–27]. More important, we supported two important indicators of inflammation response, white blood cell and IL-6 as parameters for assessing in-hospital outcome in patients with COVID-19 pneumonia. There is increasing evidence that IL-6 has become the main driver of inflammation associated with the disease. Of all tested cytokines, IL-6 is increased most significantly, with an upward trend of more than 10 times [28–29].

Among 173 patients, 19.7% had an increased LDH levels and only 10.4% had an increased creatine kinase levels. The results suggested that some patients with increased LDH levels may not myocardial injury. LDH levels may reflect tissue necrosis associated with immune hyperactivity [30]. Thus, LDH may be a useful and easy to test parameter in order to predict poor clinical outcome. Notably, antiviral treatment does not seem to improve in-hospital outcomes in this study. Even a cohort study from Italy showed that the patients receiving antiviral treatment had lower odds of discharge [31]. The results suggested that we need to use them with caution before confirming the effects of these antiviral drugs on COVID-19 pneumonia.

This study had also some limitations. First, this was a retrospective single-center study, so it might lack of high-level evidence. Next, all patients in this study were enrolled after Chinese Spring Festival travel rush, and the results might only reflect clinical characteristics of the epidemic in Wuhan during a certain period. Finally, since there were no recognized treatment guidelines of COVID-19 pneumonia, the impact of treatment on in-hospital outcome was not focused on analysis.

Conclusion

Older patients with diarrhea and lymphopenia need early identification and timely intervention to prevent the progression to severe COVID-19 pneumonia. However, older patients with leucopenia, increased lactic dehydrogenase and interleukins-6 levels are at a high risk for poor in-hospital outcome.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Hospital of Chengdu University of Traditional Chinese Medicine.

Consent for publication

Not applicable.

Availability of data and materials

The data used to support the findings of this study are included within the article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Xiao-Yu Hu, Jian-Yuan Tang and Yang Zhang designed the study, Xiao-Yu Hu, Hai Liu, Jing Chen, and Jun Xue were participated in the collection and arrangement of data, Mi Yan conducted statistical design, Fang Yang, Shao-Bo Wang and Jian-Xing Luo conducted a statistical analysis, Yang Zhang wrote the manuscript. All authors read and approved the final manuscript for publication.

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Footnotes

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Figures

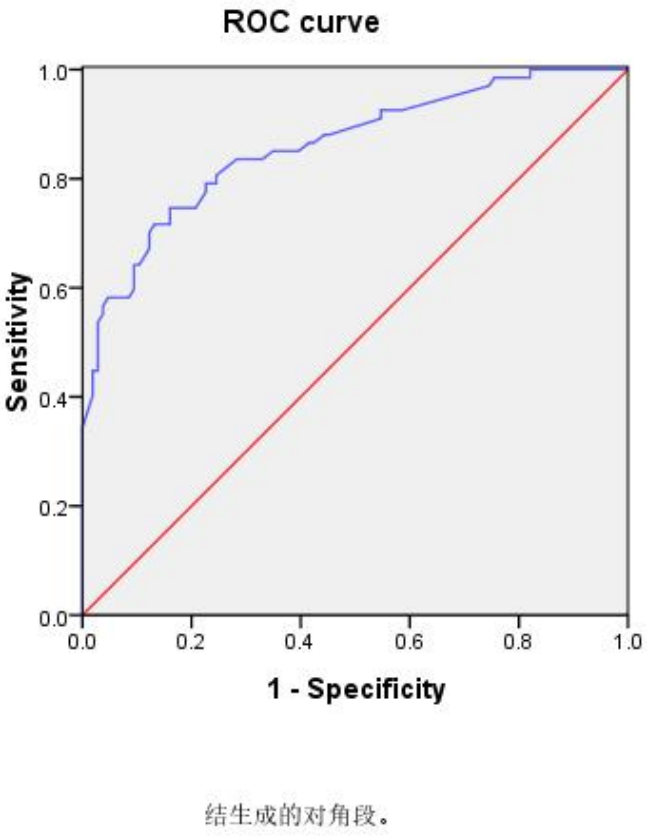
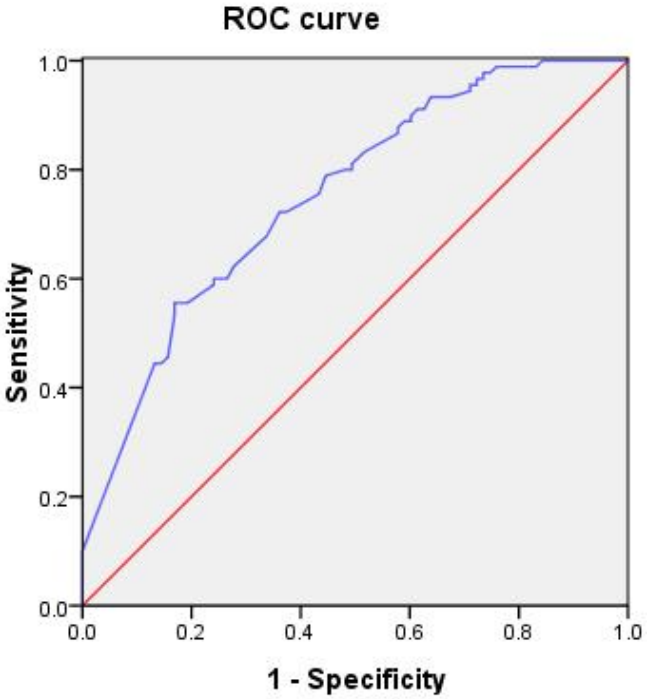


Figure 1

ROC Curve of predictive logistic regression model for disease severity of COVID-19 pneumonia. A prediction model for disease severity on admission is constructed by three indicators of age, diarrhea and lymphopenia.



结生成的对角段。

Figure 2

ROC Curve of predictive logistic regression model for in-hospital outcome in COVID-19 pneumonia. A prediction model for disease severity on admission is constructed by three indicators of age age > 65 years, leucopenia, increased LDH and IL-6 levels.