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Clinical Course and Virus Shedding of Mild and Moderate COVID-19 in South China: A Retrospective Study

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Abstract

Background: Among patients with Coronavirus pneumonia (COVID-19), those with mild-to-moderate diseases often have nonspecific features leading to delay in diagnosis and spreading of the infection. We studied patients with mild-to-moderate diseases to identify clinical, radiological and laboratory features that will facilitate early diagnosis.

Methods: This is a retrospective study of COVID-19 patients with mild-to-moderate severity who were admitted to two designated hospitals in Foshan City, Guangdong Province and discharged from January 24th, 2020 to March 10th, 2020. Demographic data, clinical features, laboratory chest CT findings, and virus shedding were collected.

Results: A total of 70 mid-to-moderate COVID-19 patients (52.9% male, mean age 40.9 ± 14.6 years) were enrolled; 52.9% were clustered cases. The average age of patients with mild symptoms was younger than those with moderate symptoms (27.0 ± 5.2 *vs.* 42.2 ± 14.5, P<0.01). Median incubation period was 5.0 (Interquartile IQR: 2.0-10.8) days. The average temperature of all patients during the first 3 days was low-grade fever. Dyspnea is uncommon (5.3%). Lactate Dehydrogenase (LDH) was elevated (456.5 ± 174.4 U/L) and serum Ca^{2+} was lowered [1.1 (IQR: 1.1-2.2) mmol/l] in all patients. Leukocyte count was normal in all patients. Chest CT abnormalities including ground glass opacification, vascular thickening, mixed lesions and consolidation were observed in 98.4%, 81.3%, 59.4%, and 6.3% of patients with moderate diseases. The worst chest CT lesions were observed at Day 10. All the COVID-19 patients had a high viral load within 11 days. The average time of nucleic acid conversion was 17.4 ± 8.2 days, with one case prolonged up to 55 days.

Conclusion: Our study revealed that low grade fever, elevated LDH, lowered calcium levels, and abnormal chest CT findings were common features in patients with mild-to-moderate COVID-19 in South China. In contrast, dyspnea was uncommon and none had abnormal leukocyte count. These findings provide important clues for clinicians to make an early diagnosis.

Keywords: COVID-19; Mild and moderate; Clinical course; Virus shedding

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Introduction

At the end of 2019, new Coronavirus pneumonia (COVID-19) epidemic caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was reported in Wuhan, Hubei, China. The World Health Organization (WHO) declared it a pandemic on March 11th, 2020.

SARS-CoV-2 is more contagious than the SARS-CoV outbreak in 2003. The number of deaths from COVID-19 is far more than from SARS and Middle East Respiratory Syndrome (MERS) [1]. The Center for Disease Control and Prevention (CDC) of China released the characteristics of 72,314 cases of COVID-19 outbreaks in mainland China, which is the largest epidemiological survey up to date. This survey has characterized mild and moderate patients accounting for 81%, which become the main source and reservoir of infection [2,3]. In addition, prolonged virus shedding was found among COVID-19 patients after the symptoms disappeared [4]. Although the epidemiology and clinical characteristics of patients with COVID-19 have been widely described, there have been no specific reports on the clinical course and virus shedding of COVID-19 patients with mild-to-moderate symptoms [2,5]. Early diagnosis of this latter group of patients is important to reduce the

risk of community spread and to offer prompt treatment.

According to the up-dated public data, Foshan is a region with a high incidence of COVID-19 in South China. In this study, we retrospectively collected 70 patients with mild-to-moderate COVID-19 to describe the clinical, radiological and laboratory characteristics to correlate with virus shedding during the course of the disease.

Materials and Methods

Evidence before this study

We searched studies documented mild and moderate COVID-19, in PubMed up to April 03rd, 2020, using the following keywords: "novel coronavirus" or "SARS-CoV-2" or "COVID-19" and "mild type" or "Common type" or "mild" or "moderate" and "viral shedding". We did not impose time and language restrictions. Only two small-scale clinical observational studies were identified [6,7].

Study design and participants

This retrospective study enrolled COVID-19 patients with mild-to-moderate symptoms confirmed by Polymerase Chain Reaction (PCR) who were admitted into two designated hospitals in Foshan City, Guangdong Province, and discharged from January 24th, 2020 to March 10th, 2020. Both diagnosis and discharge criteria were according to the second to seventh editions of the "New Coronavirus Pneumonia Diagnosis and Treatment Program" issued by the National Health Commission of China. The study has been approved by the Ethics Committee of the First People's Hospital of Foshan City and the Fourth People's Hospital of Foshan City, which fulfilled the 1964 Helsinki Declaration and its subsequent amendments.

Data collection

One researcher was responsible for extracting all the data from electronic medical records and the CDC in Foshan City, and two other researchers independently reviewed the accuracy of the data. Comorbid conditions included: Chronic obstructive pulmonary disease, diabetes, hypertension, coronary heart disease, chronic kidney disease, tumor, cerebrovascular disease, hepatitis B infection, and acquired immunodeficiency syndrome.

Clinical specimens were collected for various tests from COVID-19 patients at multiple time points, which included White Blood Cell count (WBC), Lactate Dehydrogenase (LDH), C-Reactive Protein (CRP), liver and kidney functions, D-dimmer, Lactate (LAC), electrolyte, Creatine Kinase (CK), Creatine Kinase isoenzyme (CK-MB), Procalcitonin (PCT), Blood Gas Analysis (BGA), and coagulation function. CT scans of thorax were performed on all patients. The imaging features were marked for the presence or absence of four lesions: Ground-Glass Opacification (GGO), consolidation, mixed (GGO combined with consolidation), and thickened blood vessels [8]. The frequency of the above inspections and nucleic acid tests was established by medical experts. The medications were classified into antiviral drugs, immunomodulatory drugs, antibiotics, glucocorticoid, and traditional Chinese medicines.

Definition

Date of onset referred to the date when the first clinical symptoms appeared. Date of diagnosis referred to the date when the nucleic acid was positive for the first time. The incubation period referred to the duration from exposure to onset. Nucleic acid conversion days referred to the number of days that met the discharge criteria and were negative for the first nucleic acid test during two consecutive results. Fever was defined as axillary temperature ≥ 37.3°C. Continuous variable data from clinical course were taken as an average of three days. The oxygenation index P/F=PaO_2/FiO_2 was the ratio of arterial oxygen pressure to inhaled oxygen concentration.

Chest CT scans were independently assessed by two chief physicians. For each image, the assigned value of GGO was 1 or 0, consolidation was 1 or 0, mixed lesion was 2 or 0, and thickened blood vessel was 1 or 0 [8]. Only one of the first three lesions were assigned. When the results were inconsistent, a third chief physician would assess and confirmed the score. A low score indicated a good condition. According to the clinical course of COVID-19, four phases of chest CT were defined: 1st phase (1 to 4 days), 2nd phase (5 to 8 days), 3rd phase (9 to 13 days), and 4th phase (more than 14 days) [9].

Nucleic acid detection procedures

Pharyngeal swabs were transported to Foshan CDC for real-time fluorescent PCR. ORF1ab and N genes of SARS-CoV-2 were selected as amplification target regions. Designated primers and fluorescent probes were used according to the commercial kit. The cycle threshold value was related to the copy number of virus in an inverse and exponential manner. Quality control was according to the instructions of the new coronavirus nucleic acid detection kit and strict implementation. A cycle threshold value greater than 38 was defined as negative.

Statistical analysis

The Kolmogorov-Smirnov normality test (D test) was used for numerical data to test if they were normally distributed. Comparison of the mean between groups with the normal distribution was carried out using independent sample t test; non-parametric data were analyzed by Mann-Whitney U test. Pearson-χ^2 test and Fisher's exact test were used for categorical data. Bonferroni-adjusted χ^2 test was used for pairwise comparison of rates. SPSS 21.0 statistical software was used for data processing, with α=0.05 as the inspection level. The graph shown in this study was drawn by statistical software R language (3.6.1).

Results

Demographic and epidemiological characteristics

A total of 70 patients were included, the baseline characteristics of the entire and subgroup was shown in Table 1. Six cases had mild disease (8.57%), 64 had moderate disease (91.43%), the average age was 40.9 ± 14.6 years, and 37 (52.9%) were male. Among them, 52.9% were clustered cases. Regarding travel history, 58.6% patients had a history of living in Wuhan, and 60.0% had recently visited Wuhan or had contact with Wuhan residents. Only 2.9% had a history of wildlife exposure. The epidemiological classification was 77.1% for category A, 15.7% for category C, 4.3% for category B and 2.9% for category 2B. Category A referred to clear history of living in Wuhan or Recently visited Wuhan, and Category C referred to clear history of close contact with people of category A. While Category B referred to unclear history of close contact with people of category A or C, and Category 2B referred to unclear history of close contact with people of category B. The average day of clinical course was 27.7 ± 8.4; the media incubation period was 5.0 days (interquartile IQR, 2.0-10.8). The median time from onset of symptoms to the first visit from the first visit to diagnosis, and from onset of symptom to hospital admission was 1.0 (IQR, 1.0-3.0), 1.0 (IQR, 0.0-3.5), and 6.5 ± 4.2, respectively. The average age of the mild type was younger than the moderate type (27.0 ± 5.2 *vs.* 42.2 ± 14.5, t= -2.655, P=0.008), but

Table 1: Baseline characteristics of COVID-19 patients, according to mild and moderate type ¶.

	Total (n=70)	Mild type (n=6)	Moderate type (n=64)	T/Z/χ^2	P value
Baseline characteristics					
Age, Mean ± SD, y	40.9 ± 14.6	27.0 ± 5.2	42.2 ± 14.5	-2.655	0.008
Sex, no./total no (%)				0.502	0.677
Male	37/70(52.9)	4/6(66.7)	33/64(51.6)		
Female	33/70(47.1)	2/6(33.3)	31/64(48.4)		
Clustered cases, no./total no.	37/70(52.9)	5/6(16.7)	32/64(50.0)	2.446	0.203
Exposure to source of transmission within past 14 days, no./total no.					
Living in Wuhan	41/70(58.6)	5/6(83.3)	36/64(56.3)	1.658	0.389
Recently visited Wuhan	42/70(60.0)	5/6(83.3)	37/64(57.8)	1.489	0.39
Had contact with Wuhan residents	42/70(60.0)	5/6(83.3)	37/64(57.8)	1.489	0.39
Contact with wildlife	2/70(2.9)	0/6(0)	2/64(3.1)	0.193	1
The epidemiological classification, no./total no.[#]				1.859	0.572
Category A	54/70(77.1)	4/6(66.7)	50/64(78.1)		
Category B	3/70(4.3)	0/6(0)	3/64(4.7)		
Category C	11/70(15.7)	2/6(33.3)	9/64(14.1)		
Category 2B	2/70(2.9)	0/6(0)	2/64(3.1)		
Media incubation period, median (IQR), d	5.0(2.0-10.8)	4.0(2.5-30.5)	6.0(2.0-10.0)	-0.659	0.51
Day of clinical course, Mean ± SD, d	27.7 ± 8.4	26.5 ± 10.1	27.8 ± 8.3	-0.364	0.717
Onset of symptom to the first visit, median (IQR), d	1.0(1.0-3.0)	1.0(-0.3-3.0)	1.0(1.0-3.0)	-1.031	0.302
The first visit to diagnosis, median (IQR), d	1.0(0.0-3.5)	1.0(-0.5-1.0)	2.0(0.0-4.0)	-1.321	0.186
Onset of symptom to Hospital admission, Mean ± SD, d	6.5 ± 4.2	3.3 ± 3.1	6.8 ± 4.2	-1.94	0.057
Nucleic acid conversion days, Mean ± SD, d	17.4 ± 8.2	15.8 ± 4.6	17.5 ± 8.4	-0.489	0.626
Comorbid conditions, no./total no (%)					
Diabetes	1/70(1.5)	0/6(0)	1/64(1.6)	0.095	1.000
Hypertension	4/70(5.7)	0/6(0)	4/64(6.3)	0.398	1.000
Hepatitis B infection[§]	3/70(4.3)	0/6(0)	3/64(4.7)	0.294	1.000
Symptoms and Signs at admission					
Fever (>37.3ºC), no./total no (%)	47/70(67.1)	4/6(66.7)	43/64(67.2)	0.001	1.000
Headache, no./total no (%)	12/70(17.1)	1/6(16.7)	11/64(17.2)	0.001	1.000
Cough, no./total no (%)	46/70(65.7)	3/6(50.0)	43/64(67.2)	0.719	0.406
Sore throat, no./total no (%)	11/70(15.7)	0/6(0)	11/64(17.2)	1.224	0.58
Sputum, no./total no (%)	14/70(20.0)	2/6(33.3)	12/64(18.8)	0.729	0.592
Fatigue, no./total no (%)	11/70(15.7)	1/6(16.7)	10/64(15.6)	0.004	1.000
Dyspnea, no./total no (%)	4/70(5.7)	0/6(0)	4/64(6.3)	0.398	1.000
Nausea, no./total no (%)	3/70(4.3)	0/6(0)	3/64(4.7)	0.294	1.000
Vomiting, no./total no (%)	2/70(2.9)	0/6(0)	2/64(3.1)	0.193	1.000
Diarrhea, no./total no (%)	3/70(4.3)	0/6(0)	3/64(4.7)	0.294	1.000
Myalgia or joint pain, no./total no.(%)	9/70(12.9)	0/6(0)	9/64(14.1)	0.968	1.000
Chills, no/total no (%)	7/70(10.0)	0/6(0)	7/64(10.9)	0.729	1.000
Respiratory rate, median (IQR), bpm	20.0 (20.0-20.0)	20.0 (20.0-20.0)	20.0 (20.0-20.0)	-1.185	0.236
Pulse rate, Mean ± SD, bpm	86.7 ± 14.8	93.7 ± 12.0	86.1 ± 15.0	1.207	0.232
Heart rate, Mean ± SD, bpm	87.8 ± 12.4	93.7 ± 12.0	87.3 ± 12.4	1.205	0.232
Systolic pressure, Mean ± SD, mmHg	123.0 ± 12.7	121.7 ± 8.4	123.1 ± 13.0	-0.271	0.787
Diastolic pressure, Mean ± SD, mmHg	76.3 ± 9.5	72.0 ± 5.6	76.8 ± 9.8	-1.169	0.246
Laboratory examinations at admission					
CRP (≥ 10 mg/L), no./total no (%)	22/70 (31.4)	0/6 (0)	22/64 (34.4)	3.008	0.167

PCT, median (IQR), ng/ml	0.01 (0.01-0.02)	0.02 (0.01-0.02)	0.01 (0.01-0.02)	-0.457	0.648
WBC, Mean ± SD, 10^9/L	5.1 ± 1.6	4.6 ± 0.7	5.1 ± 1.6	-0.745	0.459
HGB, Mean ± SD, g/L	141.1 ± 14.0	145.8 ± 10.5	140.6 ± 14.2	0.87	0.387
NE, Mean ± SD, 10^9/L	3.0 (2.6-4.0)	2.8 (2.5-3.1)	3.1 (2.6-4.1)	-1.049	0.294
NE%, no./total no.(%)	63.4 ± 11.8	60.8 ± 3.0	63.7 ± 12.3	-0.569	0.571
LY, Mean ± SD, 10^9/L	1.3 ± 0.6	1.4 ± 0.4	1.3 ± 0.6	0.01	0.992
LY%, no./total no.(%)	26.4 ± 8.6	28.8 ± 5.7	26.2 ± 8.8	0.714	0.478
PLT, Mean ± SD, 10^9/L	210.8 ± 62.0	215.2 ± 53.3	210.4 ± 63.1	0.18	0.858
AST, median (IQR), U/L	25.0 (21.0-31.0)	20.5 (17.5-24.5)	25 (22.0-31.8)	-2.144	0.032
ALT, median (IQR), U/L	26.0 (15.0-34.5)	19.5 (9.0-29.5)	26 (15.3-37.5)	-1.428	0.153
TBIL, Mean ± SD, umol/L	12.6 ± 6.6	13.8 ± 10.3	12.4 ± 6.2	-0.168	0.867
DBIL, Mean ± SD, umol/L	6.4 ± 4.9	8.0 ± 0.0	6.3 ± 5.0	0.332	0.743
IBIL, Mean ± SD, umol/L	4.6 ± 4.4	0.0 ± 0.0	4.8 ± 4.4	-1.063	0.301
CR, Mean ± SD, umol/L	67.2 ± 20.3	71.6 ± 19.1	66.7 ± 20.5	0.562	0.576
BUN, Mean ± SD, mmol/L	4.2 ± 1.1	4.1 ± 1.0	4.2 ± 1.1	-0.211	0.833
LDH, Mean ± SD,U/L	456.5 ± 174.4	328.3 ± 43.9	468.5 ± 177.3	-1.919	0.059
PT, Mean ± SD,s	10.8 ± 0.6	11.1 ± 0.4	10.8 ± 0.7	1.042	0.301
FBG, Mean ± SD, g/L	3.2 ± 1.0	3.3 ± 2.2	3.2 ± 0.8	-1.265	0.206
K^+, Mean ± SD, mmol/l	3.8 ± 0.5	4.2 ± 0.4	3.8 ± 0.5	2.313	0.024
Na^+, Mean ± SD, mmol/l	139.8 ± 3.8	140.2 ± 2.8	139.7 ± 3.9	0.281	0.78
Cl^-, Mean ± SD, mmol/l	102.3 ± 2.7	101.6 ± 1.2	102.4 ± 2.8	-0.739	0.462
Ca^{2+}, median (IQR), mmol/l	1.1 (1.1-2.2)	2.3 (1.4-2.3)	1.1 (1.1-2.2)	-1.675	0.094
LAC, Mean ± SD, mmol/l	1.3 ± 0.7	0.9 ± 0.0	1.3 ± 0.7	-0.617	0.541
CK, Mean ± SD, U/L	52.1 ± 31.8	54.8 ± 29.2	51.8 ± 32.2	0.217	0.829
CK-MB, median (IQR), U/L	5.0 (2.0-7.5)	3.5 (1.8-5.0)	5.0 (2.0-8.0)	-1.241	0.214
D-dimmer, median (IQR), ng/mL	160 (80-460)	130 (30-770)	165 (87.5-462.5)	-1.098	0.272
Partial pressure of oxygen, Mean ± SD, mmHg	112.7 ± 42.1	89.0 ± 0.0	113.2 ± 42.4	-0.565	0.575
FiO_2, median (IQR)%	21.0 (21.0-37.0)	21.0 (21.0-21.0)	24.0 (21.0-37.0)	-0.95	0.342
oxygenation index, Mean ± SD, mmHg	378.9 ± 111.9	/&	/&	/&	/&
Antibody, no./total no (%)				0.509	0.464
positive	27/33 (81.8)	2/3 (66.7)	25/30 (83.3)		
negative	6/33 (18.2)	1/3 (33.3)	5/30 (16.7)		
CT changes in full clinical course, no./total no. (%)					
GGO	63/70 (90)	0/6 (0)	63/64 (98.4)	59.063	<0.001
consolidation	4/70 (5.7)	0/6 (0)	4/64 (6.3)	0.398	1
Mixed	38/70 (54.3)	0/6 (0)	38/64 (59.4)	7.793	0.007
vascular thickening	52/70 (74.3)	0/6 (0)	52/64 (81.3)	18.958	<0.001
Treatment					
Oxygen supplementary, no/total no (%)				2.858	0.264
No oxygen supplementary	18/70 (25.7)	1/6 (16.7)	17/64 (26.6)		
Low-flow oxygen	24/52 (46.2)	3/6 (50.0)	21/64 (32.8)		
Medium flow oxygen	13/52 (25.0)	2/6 (33.3)	11/64 (17.2)		
High-flow Nasal Cannula	15/52 (28.8)	0/6 (0)	15/64 (23.4)		
Medication, no./total no (%)					
Lopinavir	44/70 (62.9)	5/6 (83.3)	39/64 (60.9)	1.179	0.401
Arbidol	50/70 (71.4)	3/6 (50.0)	47/64 (73.4)	1.477	0.343
Chloroquine	7/70 (10.0)	1/6 (16.7)	6/64 (9.4)	0.324	0.482
Interferon alfa-2b, recombinant	60/70 (85.7)	5/6 (83.3)	55/64 (85.9)	0.03	1

Thymosin	27/70 (38.6)	1/6 (16.7)	26/64 (40.6)	1.329	0.394
Immunoglobulin	17/70 (24.3)	2/6 (33.3)	15/64 (23.4)	0.292	0.628
Antibiotics	53/70 (75.7)	2/6 (33.3)	51/64 (84.4)	6.41	0.028
Quinolones	51/70 (72.9)	2/6 (33.3)	49/64 (76.6)	5.184	0.042
Cephalosporins	11/70 (15.7)	0/6 (0)	11/64 (17.2)	1.224	0.58
Hydrocarbons	3/70 (4.3)	0/6 (0)	3/64 (4.7)	0.294	1
XueBiJing$	8/70 (11.4)	0/6 (0)	8/64 (12.5)	0.847	1
Traditional Chinese medicines	54/70 (77.1)	6/6 (100)	48/64 (75.0)	1.825	0.327
Glucocorticoid	7/70 (10.0)	0/6 (0)	7/64 (10.9)	0.729	1.0

CRP: C-Reactive Protein; WBC: White Blood Cell Count; HGB: Hemoglobin; NE: Neutrophil Count; NE%: Neutrophil Percent; LY: Lymphocyte Count; LY%: Lymphocyte Percent; PLT: Platelet Count; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; TBIL: Total Bilirubin; DBIL: Direct Bilirubin; IBIL: Indirect Bilirubin; CR: Creatinine; BUN: Blood Urea Nitrogen; LDH: Lactate Dehydrogenase; K+: Potassium; Ca2+: Calcium; Na+: Sodium; Cl-: Chlorion; CK: Creatine kinase; CK-MB: Creatine Kinase Isoenzyme; FiO2: Oxygen Concentration; LAC: Lactate; PT: Prothrombin Time; FBG: Fibrinogen; PCT: Procalcitonin

¶For the numerical data with normal distribution, Mean ± SD was expressed; for the numerical data with normal distribution but uneven variance or non-normal distribution, median (IQR) was expressed. Percentages may not total 100 because of rounding.SD Standard Deviation, IQR interquartile range.

#Category A: Clear history of Living in Wuhan or Recently visited Wuhan; Category B: Unclear history of close contact with people of category A or C; Category C: Clear history of close contact with people of category A; Category 2B: Unclear history of close contact with people of category B.

§The presence of hepatitis B infection was defined as a positive result on testing for hepatitis B surface antigen with or without elevated levels of alanine or aspartate aminotransferase.

ǂ For LDH, normal range is 115 U/L to 290 U/L

ǁ For Ca2+, normal range is 2.1 mmol/l to 2.55 mmol/l

&limited data incapable to be counted

$ A Chinese medicine injection, which has the effect of antagonizing endotoxin *in vitro*. The main component is safflower yellow pigment A

Table 2: The proportion of each lesion in four phases of chest CT.

	1-4d	5-8d	9-13d	More than 14d	P value
GGO					<0.001
Yes	11 (47.8)	17 (34.7)*	21 (34.4)&	84 (63.6)*&	
No	12 (52.2)	31 (65.3)	40 (65.6)	48 (36.4)	
Consolidation					0.311
Yes	0 (0)	0 (0)	3 (4.8)	3 (2.3)	
No	23 (100)	48 (100)	58 (95.2)	129 (97.7)	
Mixed					0.001
Yes	5 (21.7)	23 (47.9)§	32 (52.5)#	35 (26.5)# §	
No	18 (78.3)	25 (52.1)	29 (47.5)	97 (73.5)	
Vascular thickening					0
Yes	10 (43.5)※	34 (70.8)	51 (83.6)※¶	71 (53.8)¶	
No	13 (56.5)	14 (29.2)	10 (16.4)	61 (46.2)	

GGO: Ground-Glass Opacification; mixed (GGO combined with consolidation). Among them, comparison in pairs were shown as:

*The proportion of GGO in 14 days later was significantly higher than 5-8 days (63.6% *vs.* 34.7%, P <0.001); &The proportion of GGO in 14 days later is significantly higher than 9-13 days (63.6% *vs.* 34.4%, P<0.001)

§The proportion of mixed changes in 5-8 days was significantly higher than that of 14 days later (47.9% *vs.* 26.5%, P=0.011)

#The proportion of mixed changes in 9-13 days was significantly higher than that of 14 days later (52.5% vs. 26.5%, P=0.001)

※The proportion of vascular thickening changes in 9-13 days was significantly higher than that of 14 days later (83.6% *vs.* 43.5%, P=0.001)

¶The proportion of vascular thickening changes in 9-13 days was significantly higher than that of 14 days later (83.6% *vs.* 53.8%, P<0.001)

there was no significant difference between the two groups in other characteristics.

Clinical characteristics

There were 11.4% COVID-19 patients had one or more comorbid conditions, including hypertension (5.7%), hepatitis B virus infection (4.3%) and diabetes (1.5%), all of who were patients of moderate type. Common symptoms were fever (67.1%) and cough (65.7%), while sputum (20.0%), headache (17.1%), sore throat (15.7%), fatigue (15.7%), myalgia or joint pain (12.9%), dyspnea (5.7%), nausea (4.3%), vomiting (2.9%) and diarrhea (4.3%) were relatively rare (Table 1).

The average temperature of all patients in the first 3 days was low-grade fever, and moderate type showed higher temperature than the mild type [Supplementary Figure 1(a), 1(b)], but the trend disappeared afterwards.

Laboratory results

The laboratory results at the time of admission were shown in Table 1. Only LDH and serum Ca^{2+} were abnormal in all patients, with LDH level higher (456.5 ± 174.4 U/L) and serum Ca^{2+} level lower [1.1 (IQR: 1.1-2.2) mmol/l] than normal. The level of AST in moderate type was higher than that in mild type [25 (IQR: 22.0-31.8) U/L *vs.* 20.5 (IQR: 17.5-24.5) U/L, Z= -2.144, P=0.032], and serum K^+ in moderate type was lower than that in mild type (3.8 ± 0.5 mmol/l *vs.* 4.2 ± 0.4 mmol/l, t=2.313, P=0.024). LDH increased throughout the clinical course and, peaked at Day 9 to 12. LAC showed the same trend at Day 9 to 12. D-dimmer presented four peaks from Day 3 to 27 (Figure 1a-1c). Serum Ca^{2+} returned to normal range by Day 15 (Figure 1d). CRP peaked at Day 6 to 15 (Figure 1e).

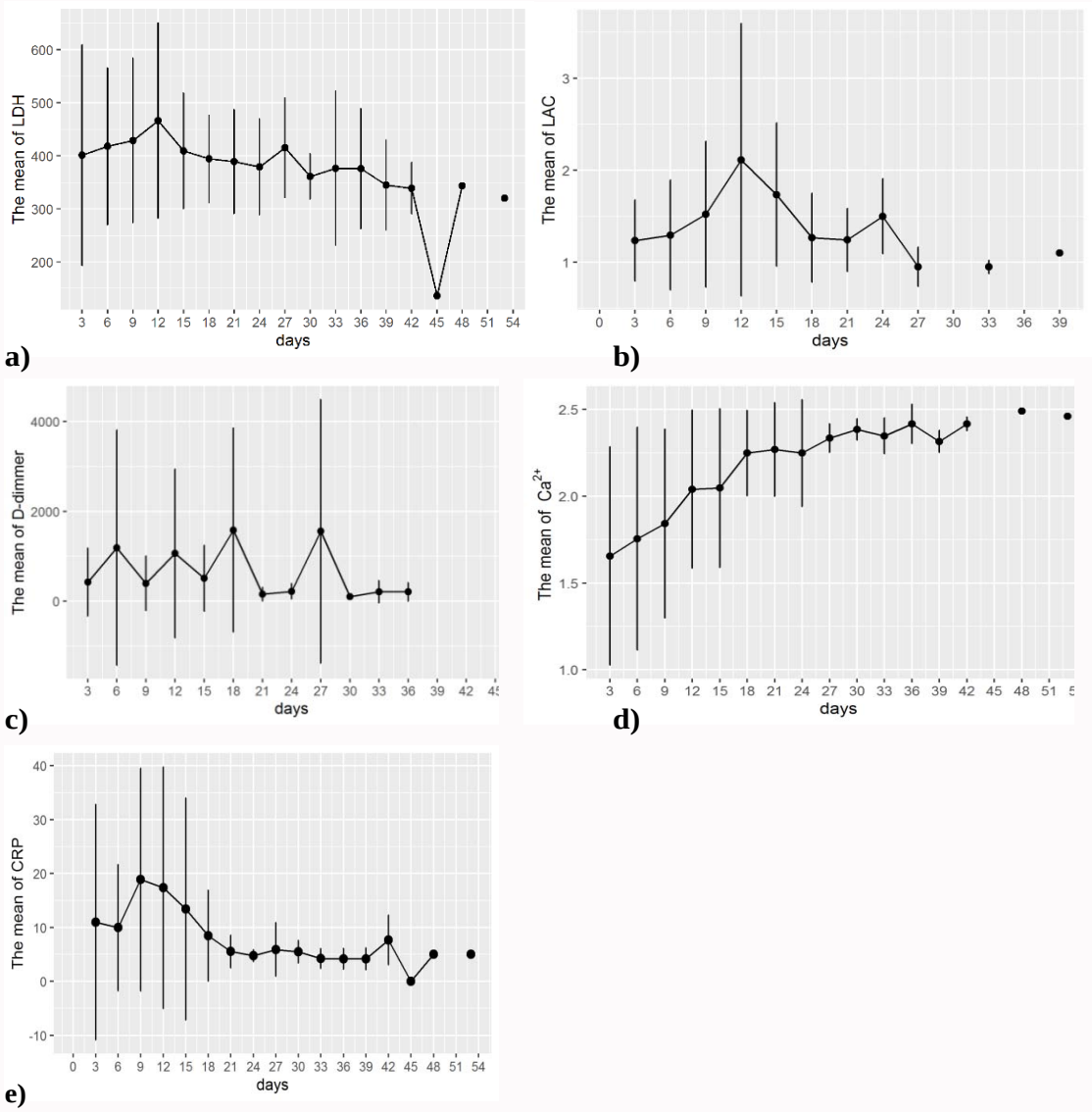


Figure 1: The overall trend of laboratory examinations in clinical course. The continuous variable data from clinical course was taken as an average of three days. LDH: Lactate Dehydrogenase; LAC: Lactate; Ca2+: Calcium; CRP: C-Reactive Protein

Characteristic of chest CT changes

No changes were observed in patients with mild diseases. In 64 cases of moderate type, GGO, vascular thickening, mixed lesions and consolidation accounted for 98.4%, 81.3%, 59.4%, and 6.3%, respectively.

The changes of each lesion in four phases were shown in Table 2. The maximal GGO changes were highest after Day 14. While mixed lesions and vascular thickening showed the maximal changes in 9 to 13 days. Chest CT changes did not return to normal even when the patients have recovered clinically (Figure 2).

Virus shedding pattern

The average clinical course was 27.7 ± 8.4 days, and the nucleic acid conversion time was 17.4 ± 8.2 days (Table 1) with 90% patients had PCR conversion in 26 days. We analyzed pharyngeal swab specimens in all patients, the result of which included qualitative data (negative, positive, suspicious, Figure 3) and quantitative data (CT value, Figure 4). Nucleic acid positivity was high within first 10 days and decreased significantly from Day 11 to 14 (Figure 3). We found a case of virus shedding for up to 55 days, as shown in a red curve (Figure 4).

The patterns of the N value of the viral shedding of pharyngeal swabs were the same as the O value (Supplementary Figure 2).

Discussion

We studied patients with mild-to-moderate diseases to identify clinical, radiological and laboratory features that will facilitate early diagnosis of COVID-19. The average age of all patients was 40.9 ± 14.6 years with 53% male. The median incubation period was 5.0 days, the median time from onset of symptom to first visit was 1.0 day, and the mean time from onset of symptom to hospital admission was 6.5 ± 4.2 days. This was consistent with the current research on COVID-19 in China [2,5,10,11]. We found the average temperature of all patients in the first 3 days was low-grade fever with mild-to-moderate diseases. Fever either subsided or became intermittent in about 40% of patients during the subsequent course of the disease.

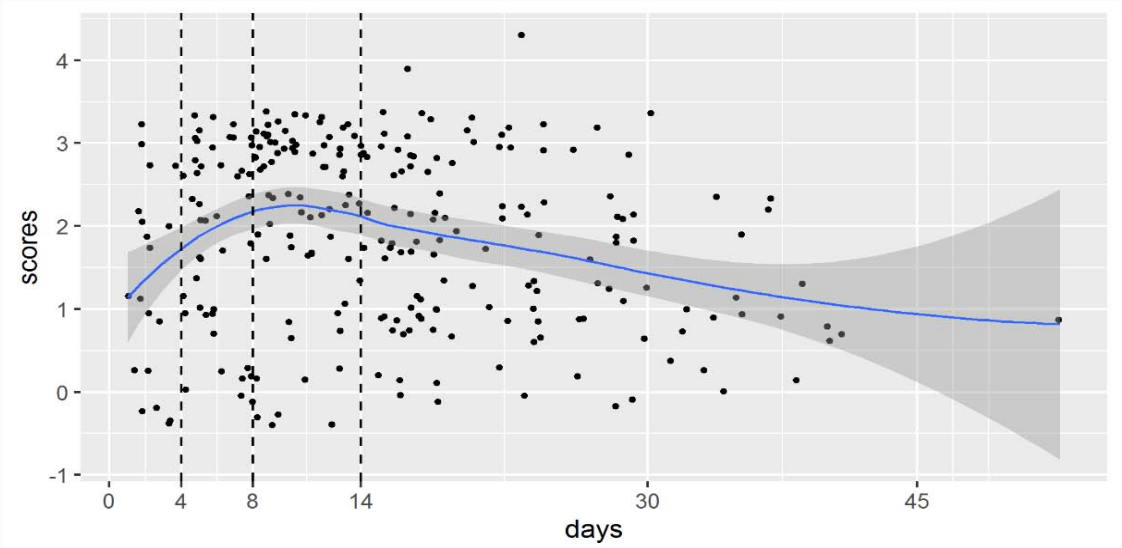


Figure 2: The overall trend of scores showing degrees of lesions involvement in four phases of chest CT images in clinical.

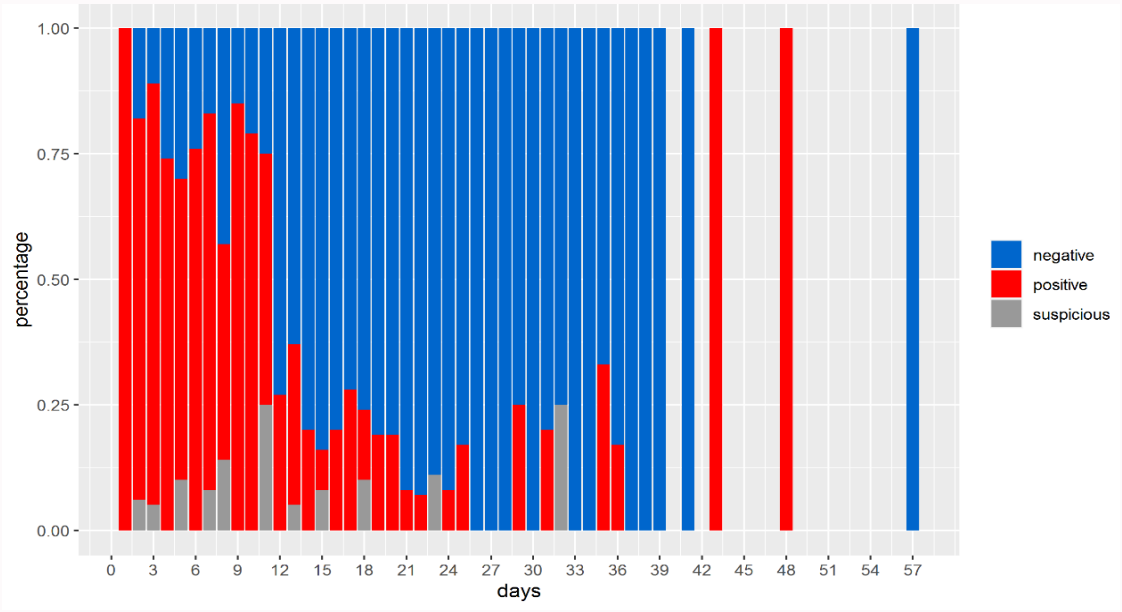


Figure 3: The trend of qualitative percentage of virus shedding with pharyngeal swabs.
In the graph showing the qualitative CT value of virus shedding, which indicated the proportion of negative, positive and suspicious of nucleic acid in each day of clinical course in all patients. Nucleic acid positivity was high within first 10 days and decreased significantly from Day 11 to 14.

Therefore, frequent monitoring of body temperature in patients presenting with non-specific symptoms is important to increase our alertness to COVID-19. Only a small proportion of our patients had dyspnea, 5.7% compared with 34.5% reported in one study [12], indicating that dyspnea was rare in mild-to-moderate COVID-19. This is consistent with the fact that we did not find any significant desaturation in our study.

All our patients had elevated LDH and lowered serum Ca^{2+} levels. Ca^{2+} decreased within 14 days, with the moderate type more apparent than the mild type. We previously found that elevated LDH is an independent risk factor for progression to critical illness in COVID-19 patients [13]. A prospective observational study also showed LDH>246 IU/L, Ca^{2+} <2.18 mmol/L were two independent risk factors for CAP death [14]. It was speculated that LDH and LAC were more sensitive markers of anaerobic glycolysis than oxygenation index, with LDH superior to LAC. In contrast, WBC, lymphocytes, liver and kidney function, myocardial enzymes, and coagulation function were in normal range, suggesting that the latter ones are not markers of mild and moderate COVID-19 in the early stage. In the absence of any clinical bleeding and thrombotic complications, elevated D-dimmer levels suggested the presence of subclinical hypercoagulable state and secondary hyperfibrinolysis in the first 4 weeks. Elevated D-dimer has been reported to be a risk factor for the development of COVID-19 towards ARDS (Acute Respiratory Distress Syndrome) and death [15]. The pathological mechanism might be dysfunction of endothelial cells caused by infection, leading to excessive thrombin generation and strike of fibrinolysis, the hypercoagulable state of which is more pronounced

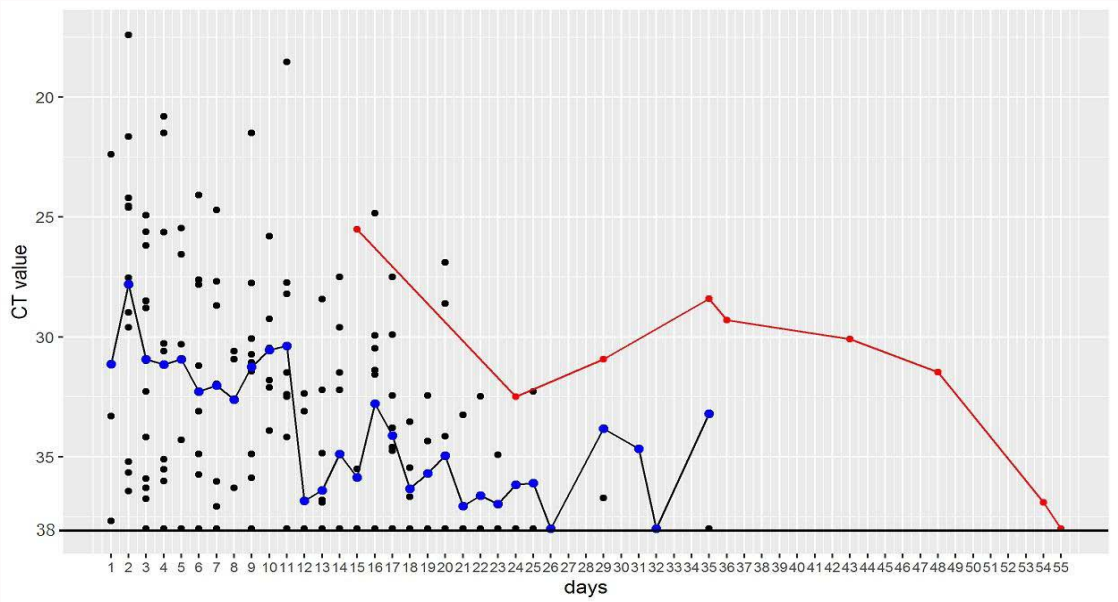
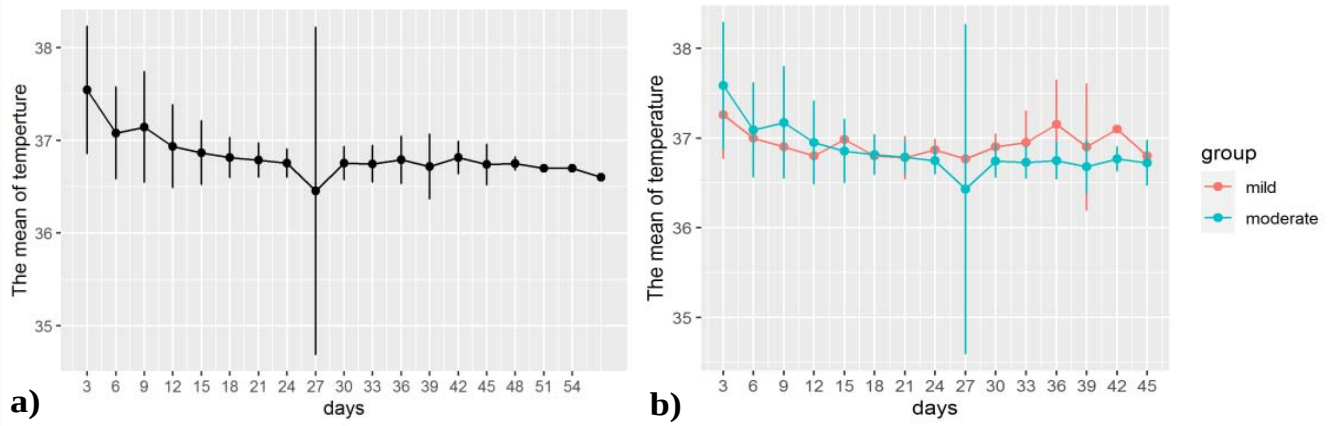


Figure 4: The trend of quantitative CT value of virus shedding with pharyngeal swabs (O value).
In the graph showing the quantitative CT value of virus shedding, in which the black dots indicated scatter plots of each O value, and the blue dots indicated the average value of O value of each day. CT value was relatively low within first 11 days. In Day 12-30, the CT value increased sharply, fluctuating in the graph. The red curve indicated a case of virus shedding for up to 55 days. Color should be used.



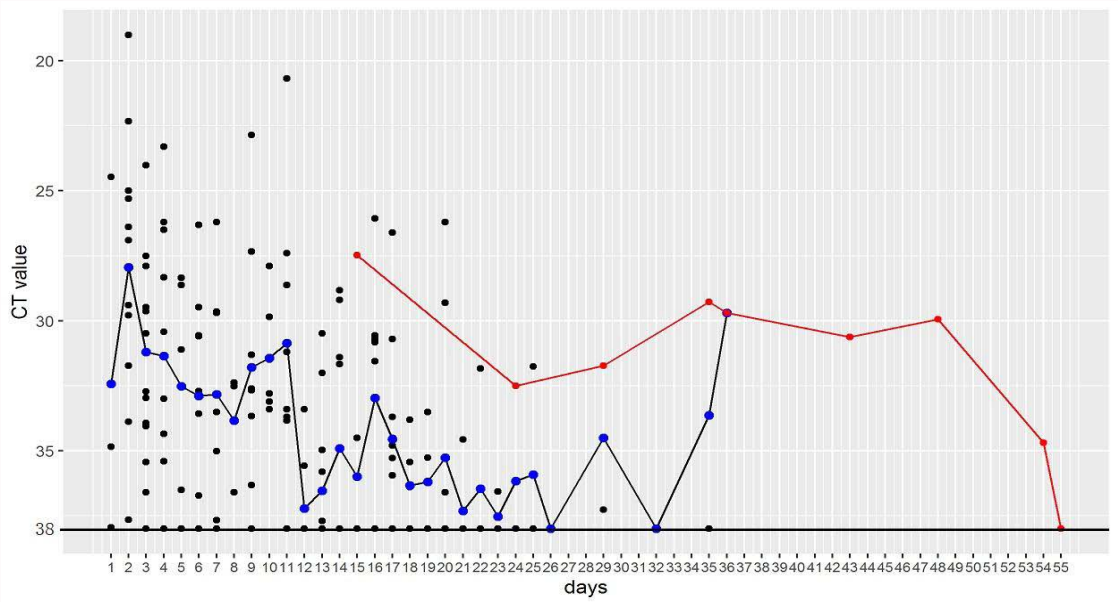
Supplementary Figure 1: The overall trend of temperature in clinical course. The continuous variable data from clinical course was taken as an average of three days.
In graph (a) showing the trend of temperature in all COVID-19 patients; (b) showing the trend of temperature in mild and moderate subgroup types of COVID-19 patients respectively.

in COVID-19 than other severe pneumonia [16]. In short, the results of serial laboratory examination being observed in our study not only confirmed the hypothetical pathogenesis of COVID-19 by Cao et al., but also provided detail time point of hypoxia, inflammation, imbalance of coagulation in mild and moderate COVID-19 [17].

We have identified important chest CT findings for moderate COVID-19. GGO lesions were most common followed by vascular thickening, which was higher than previously reported [5]. Older patients (≥ 41 years) tended to have more severe GGO and vascular thickening lesion, which was inconsistent with previous studies [16]. We also found that the worst changes of CT image on the 10th day of the clinical course in mild and moderate COVID-19 [9]. GGO lesions could still appear after 14 days, while mixed lesions and vascular thickening lesions did not increase after 9 to 13 days. Taken together, the four lesions of chest CT overlapped on Day 10, and the clinical course of GGO lesions was longer than mixed and vascular thickening lesions.

Mild and moderate COVID-19 patients had a relatively high viral load within first 11 days. The average time of nucleic acid conversion was 17.4 ± 8.2 days, which was shorter than reported of 19.5 to 24 days [6,18,19]. 90% patients were observed PCR conversion negative in 26 days. Except for one case, all patients became negative within 35 days. The positive rate of nucleic acid accounted for a high proportion within 10 days and decreased significantly from 11 to 14 days.

Our study had limitations. Firstly, the data of virus shedding is limited by the frequency of specimen collection. Secondly, we analyzed nucleic acid specimens from pharyngeal swabs only, but not from nasopharynx and lower respiratory tract, which may lead to bias in the analysis of our results. Thirdly, recall bias would inevitably



Supplementary Figure 2: The trend of quantitative CT value of virus shedding with pharyngeal swabs (N value).
In the graph showing the quantitative CT value of virus shedding, in which the black dots indicated scatter plots of each N value, and the blue dots indicated the average value of O value of each day. CT value was relatively low within first 11 days. In Day 12-30, the CT value increased sharply, fluctuating in the graph. The red curve indicated a case of virus shedding for up to 55 days. Color should be used.

affect the accuracy of the clinical data.

In conclusion, our study indicated that low-grade fever, absence of dyspnea, elevated LDH, lowered calcium levels, and abnormal chest CT findings were common features in patients with mild-to-moderate COVID-19. These findings provide important clues for clinicians to make an early diagnosis.

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