

Dynamic Clinical Features During the Para-Exacerbation Period of Critical COVID-19 Patients

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Research

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Abstract

Background COVID-19 has been currently spread all over the world with high mortality reported in severe COVID-19 patients. Many severe COVID-19 patients exacerbated from mild illness several days after hospital admissions. Pathophysiological evolution within this para-exacerbation period remain unclear.

Methods Twenty-two confirmed COVID-19 patients who underwent at least one exacerbation were included. Epidemiological, clinical, laboratory, and radiological data were extracted from electronic medical records and compared between the records of hospital admission day and the exacerbation day. Dynamic profiles of critical parameters were explored during the para-exacerbation period.

Results Most of the patients were elder (67, IQR63-79), male (81.8%), coexisted with comorbidities (72.7%), multi-segments radiologically involved and exacerbated from mild to severe illness with anoxia at a median interval of 4 days (IQR, 2-7) from hospital admissions. On exacerbations, various clinical parameters were worsened, including respiratory rate, PaO₂/FiO₂ rate (PFR), alveolar-arterial PO₂ difference (A-aDO₂), hematological cellularities, biochemical parameters and radiological abnormalities. Dynamic profiles showed that neutrophil/lymphocyte ratio (NLR), and serum level of lactic acid, lactate dehydrogenase and coagulation parameters started to increase even at four days before the exacerbation.

Conclusions Anoxia due to impaired gas exchange progress pathophysiologically characterized the exacerbation of COVID-19 patients. Continuously monitoring crucial clinical parameters, such as NLR, serum albumin, LDH, lactic acid, and CT involvement scale will be helpful to improve the recognition of the disease progression in patients with COVID-19 at early stage.

Trial registration: This retrospective study has been registered in Chinese Clinical Trial Registry (ChiCTR2000030580, www.chictr.org.cn)

Introduction

In late December 2019, a group of patients were diagnosed for pneumonia of unknown cause, which were subsequently confirmed to be a novel coronavirus, known as 2019-nCoV initially and renamed for SRAS-CoV2 recently, in Wuhan, Hubei province, China(1, 2). The World Health Organization (WHO) has declared coronavirus disease 2019 (COVID-19) a public health emergency of international concern on 31st January, 2020(3). And up to date, this infectious disease has spread to more than 200 countries, infected about 7,600,000 patients and caused 420,000 death globally(4). The latest overall death rate of COVID-19 patients on mainland of China were about 5.6% according to official statistics(5), which is higher than the overall mortality rate (1.4%) reported in a study enrolled 1099 COVID-19 patients before January 29, 2020(2). In this study, of all the COVID-19 patients, 15.7% (173/1099) were in severe status, and the death rate of these severe cases was as high as 15% according to the epidemiology data(2). It has been observed in a previous study that elder people, especially those with multiple comorbidities are more vulnerable to develop severe illness after being infected with SARS-CoV2(6). This study also reported that

36 (26.1%) of 138 COVID-19 patients were transmitted to intensive care unit (ICU) at a median interval of 1 day [interquartile range (IQR) 0-3], which means that part of these ICU patients endured different time of illness progression in the para-exacerbation period. Whether or not this progression process can be predicted and hence be interfered in will play decisive roles in the management of COVID-19 patients, for most of deaths and heavy healthcare burden occurred in severe illness.

Though numerous data have compared the clinical characteristics between severe and non-severe COVID-19 patients, which may help physicians to identify the severe cases, it is by far not known how the pathophysiologic parameters evolve when a patient's status turned from mild to severe. The aim of this study was to investigate the alterations of the clinical characteristics during the para-exacerbation period in patients with COVID-19.

Methods

Data collection

We conducted a retrospective study focusing on 22 severe COVID-19 patients who received ICU care in the Shanghai Public Health Clinical Center, which is authorized for treating COVID-19 disease by the government of Shanghai City. The diagnose of these patients have been confirmed by clinical symptoms, CT findings, determined contact history and positive RT-PCR tests for SRAS-CoV2 sequences on the throat swab samples before admission. The medical data of these patients were extracted before Feb 17, 2020, and analyzed by the research team of the Department of Respiratory and Critical Care Medicine, Shanghai General Hospital affiliated to Shanghai Jiao Tong University. Epidemiological, clinical, laboratory, and radiological characteristics data were obtained from electronic medical records. Information included demographic data, medical history, coexisting comorbidities, symptoms, signs, laboratory findings, chest computed tomographic (CT) scans was collected at the time of being admitted into the hospital and the time of being exacerbated, respectively.

Details of CT images were described according to findings on the following aspects, including ground-glass opacity (GGO), local lung consolidation, fiber stripe opacities, peripheral bronchiectasis, visceral pleura involvement, pleural effusion and thickening of interlobular septal, interlobar fissure, and peripheral pulmonary artery. The infiltrated segments were counted and the infiltration scale of each segment was evaluated by a scoring system, which was defined as 0: non-infiltrated, 1: the number of GGO nodules/patches ≤ 3 or the total infiltrated area $< 1/2$ segment, 2: the number of GGO nodules/patches > 3 or the total infiltrated area $> 1/2$ segment, 3: whole segments infiltrated.

The date of disease onset was defined as the day when symptoms were noticed. The definition of exacerbation was defined as the needs for the escalation of oxygen supply due to anoxia. For all these patients, the Glasgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA), and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were determined on the day of hospital admission and the exacerbation, respectively. PaO_2 to FiO_2 rate (PFR), alveolar-arterial PO_2 difference (A-

aDO₂), neutrophil to lymphocyte ratio (NLR) were calculated based on the original data. The accurate date from onset of disease, hospital admission, and exacerbation episodes were recorded, respectively.

This retrospective study has been registered in Chinese Clinical Trial Registry (ChiCTR2000030580, www.chictr.org.cn), was approved by the Shanghai Public Health Clinical Center Ethics Committee (No. YJ-2020-S015-01) and exempted from the need for written informed consent from patients for emerging infectious disease.

Statistics

Categorical variables were described as frequency rates and percentages, and continuous variables were described using median, and interquartile range (IQR) values. Means for continuous variables were compared using pairing group *t* tests when the data were normally distributed; otherwise, the Mann-Whitney test was used. Paired comparisons were performed on the data from 20 patients that exacerbated at least 1 day after hospital admission. Proportions for categorical variables were compared using the Fisher exact test. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 13.0 software (SPSS Inc). For unadjusted comparisons, a 2-sided α of less than .05 was considered statistically significant.

Results

Presenting Characteristics

This study population included 22 hospitalized patients with confirmed NCIP and underwent at least one exacerbation. Of all the patients, 18 (81.8%) were male, 4 (18.2%) were female. The median age was 67 years (IQR, 45-79). The most common symptoms at the onset of illness were fever (22 [100%]), followed by dry cough (8 [36.4%]), expectoration (7 [31.8%]), short breath (6 [27.3%]), etc. The most common worsened symptoms at exacerbations were dyspnea (22[100%]), followed by exaggerated fever (10[45.5%]). Sixteen of 22 (72.7%) patients had 1 or more comorbidities, among them hypertension (14 [63.6%]) was most common, followed by cardiovascular disease (10 [45.5%]), etc. (table 1)

Of these patients, there were 26 exacerbation episodes together, including 19 (73.1%) had one, 2 (7.7%) had twice, 1 (0.3%) had three times of exacerbation. The median durations from the onset of illness to the hospital admission and to the first exacerbation episode were 4 days (IQR, 2-8) and 10 days (IQR, 4-11), respectively. Except two patients being incubated immediately after being hospitalized, of the other 20 patients, the median durations from hospital admission to the first exacerbations were 4 days (IQR, 2-7). In the first exacerbation episode, 10 of 22 (75%) received intubation and mechanical ventilation, 8 (36.4%) received Hi-Flow oxygen therapy, 4 (18.2%) received extracorporeal membrane oxygenation (ECMO) (table 1).

After admission, 13 of 22 (59.1%) patients received glucocorticoids, 11 (50%) received one and 7 (31.8%) received two kinds of antiviral drugs. Other treatment included immunomodulating drugs such as

Thymopeptide and human immunoglobulin, antibiotics, low molecular weight heparin, and Chinese traditional medicines were applied (table 1).

Vital Signs and Laboratory Parameters on hospital admissions and exacerbations

Statistically significant difference of respiration rate, but not of temperature, heart rate, and mean arterial pressure, can be found in between the two recording days. Numerous significant differences in laboratory findings were found in between the two recording days as well, including higher white blood cell (WBC) and neutrophil, lower lymphocyte counts, lower NLR, as well as higher levels of fibrinogen, fibrinogen degradation product (FDP), D-dimer, vein lactic acid, lactate dehydrogenase (LDH), proBNP, and lower albumin, hematocrit. For calculative indexes, PFR was lower, A-aDO₂, APACHE II and SOFA were higher, while GCS remained similar on the exacerbation day. The values of CD3 (266.5[116-558.8]), CD4 (141[75-282]), and CD8 (122[29-284]) were below the lower limits of each normal range (table 2).

Dynamic profile of critical laboratory findings in severe COVID-19 patients

To determine the profile of dynamic changes of some hematological and biochemical parameters that critically involved in the disease progression, clinical data were extracted at four timepoints, i.e. 7 days before, 4 days before, 2 days before and the due day of the first exacerbation and integrated into line charts. Data of 7-day-before were from 4 patients, data of 4-day-before were from 11 patients, data of 2-day-before were from 16 patients, and data of exacerbation day were from all the 22 patients. For hematological parameters, ascendant lines on white blood cell and neutrophil counts, a descendant line on lymphocyte count were observed. For coagulation parameters, the ascendant trends of the line were much slight. For chemobiological parameters, most of lines were ascendant prominently at the 4-day-before timepoint and remained on high level till exacerbation day, except for the line of LDH, which showed another ascendancy from the 2-day-before to the exacerbation day. For the line on albumin data, it was slightly descendant from the 4-day-before to the exacerbation day (figure 1).

Radiological findings on hospital admissions and exacerbations

Of all 22 patients, 18 had done CT scans both on the day of hospital admission and the day of exacerbations. GGO was the most common CT finding (18[100%]) on both the hospital admission and the exacerbation day, which was also the case in terms of peripheral bronchiectasis (18[100%]), visceral pleura involvement (18[100%]), and thickening of peripheral pulmonary artery (18[100%]). Local lung consolidation was found in 2 (11.1%) on hospital admission day but in 18(100%) on the exacerbation day of all 18 patients. Thickening of interlobar fissure can be found in 6 (33.3%) on hospital admission day but in 14(77.78%) on exacerbation day of all 18 patients. Pleural effusion was not found in any patients at any time (table 2).

Multiple lung segments were involved in the lung of COVID-19 patients. In current study, the mean involved segments of these patients on the hospital admission (14[IQR 10-16]), was significantly lower than those on their exacerbations (18[IQR 18-19], $t=3.75$, $p=0.013$). The lung infiltration scale of these

patients on the hospital admission (14[IQR 12-21]) was significantly escalated on their exacerbations (31[IQR 30-37], $t=4.89$, $p=0.004$), and it was also the case regarding the ventral parts of lung (including upper lobes of both sides and right middle lobe) and the dorsal parts of lung (including lower lobes of both sides). Particularly, the infiltrations in dorsal parts of lung were more serious than those in the ventral parts ($t=2.91$, $p=0.033$) on the day of exacerbations, but not on the day of hospital admission ($t=0.13$, $p=0.9$) (data not shown). Typical change in CT images of one patient were showed in figure 2.

Discussion

This cohort characterized a small group of COVID-19 patients who underwent at least one episode of exacerbation. The majority of these patients (20/22, 90.9%) were categorized as mild illness on initial diagnosis and suffered a sudden exaggeration at a median interval of 4 (IQR, 2-7) days from being hospitalized, and a median interval of 10 days (IQR, 4-11) from the onset of symptoms. Though various kinds of initial comprehensive treatments, including immunomodulators and antiviral drugs, etc. being applied on these patients when they were admitted, the exacerbations unstopably happened in a manner being unpredictable. The outcomes of exacerbations were serious, for 10 of 22 (45.5%) patients received intubation and mechanical ventilation, and even one patient was directly treated with ECMO, immediately after the first exacerbation. Identifying the underlying driving factors or potential predictive signs of such exacerbations bears immense clinical meanings to form more meticulous and effective therapeutic strategy.

Epidemiological data showed that these patients were all elders (67, IQR:63-79) and most of them are male (81.8%). Fever (defined as $T>37.3^{\circ}\text{C}$) was accompanied by all the patients on admission and worsened in 10 (45.5%) patients on the day of exacerbations, given various kinds of antipyretic medications being applied, which indicates the persistent inflammation, either induced by SARS-CoV2 infection or subsequent immune response, throughout the whole para-exacerbation period. In addition to fever, dyspnea symptom was as well presented in all patients at the day of exacerbations, which led to a reasonably high frequency of respiration rate at this stage. The dyspnea symptom was driven by a remarkably anoxia, which witnessed by the significantly decreased PFR in this group of patients on exacerbations compared with the data at hospital admissions (68.5 [64.1-95.2] vs. 315.2 [178.5-446.5], $p<0.001$). From a pathophysiological mechanism perspective, it can be safely induced that anoxia might attribute to the abnormal alveolar gas exchange process rather than the ventilation process, for PaCO_2 remained unchanged while A-aDO_2 significantly increased on exacerbation day in comparison to the data at admissions (494 [335-534] vs. 100[39.9-168], $p<0.001$).

The deteriorated abnormalities in gas exchange process that occurred on exacerbations can be explained by radiological progresses on CT images. As previous reported, ground glass opacity (GGO) was the most common abnormality in CT images of severe and nonsevere COVID-19 patients (2, 6-8), and increasing number of lung segments were involved along with the prolonged intervals from the time of illness onset (9, 10). Consistently in this cohort, GGO was universally observed, and a median of 14 segments were involved in the CT images that conducted at hospital admission, while 19 segments were involved at

exacerbations. Furthermore, the increased CT image scores on the exacerbation stage indicate that not only more segments, but also larger area was involved. Dorsal parts were more frequently involved than those in ventral parts of lung (19.8 ± 5.19 vs. 16.5 ± 3.56 , $t = -2.911$, $p = 0.033$) on exacerbations, but not differ on admissions. Early pathological examination on para-tumor lung tissue examination of two asymptomatic COVID-19 patients who received lung lobectomies for pulmonary malignancy revealed that edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration can be found in the area presented with radiological abnormalities(11), which may no doubt impair the gas exchange progress. Besides, the sign of local lung consolidation in CT images were more frequently observed on exacerbations. According to a recent unpublished pathologic study on a whole right lung from a severe COVID-19 patient received lung transplantation, haemorrhagic necrosis was found in the outer edge of gross lung sample(12), which is geographically compatible with the distribution of local lung consolidation. Thus, the emerged and/or enlarged consolidation area might also contribute to the gas exchange progress. Furthermore, the radiological sign of thickening of pulmonary peripheral artery was universally presented in the GGO-involved area on CT images of patients with COVID-19, reflecting the expansion of small vessels either by dilation from inflammatory factors or by occlusion from microthrombosis, both of which may exaggerate the abnormal ventilation/perfusion ratio (V/Q). Microthrombosis has been substantiated by the pathological finding in whole lung biopsy that reported recently on an unpublished article(12). It can also be clinically clued from the significant increases in both d-dimer and FDP of COVID-19 patients in current cohort. In this sense, anticoagulation strategy such as the use of heparin or low molecular heparin is recommended in an expert consensus for the treatment of severe COVID-19 patients(13). Taken together, the rapidly developed anoxia is probably due to the worsened gas exchange process, which can be clued from changes on $A-aDO_2$ as well as the radiological progress, representing the main typical pathophysiological characteristics of COVID-19 patient exacerbations.

In parallel with anoxia on the day of exacerbations, numerous clinical parameters deteriorated from the level of the day on hospital admissions. Though lot of previous studies have reported numerous abnormal clinical tests in COVID-19 patients, and the differences between mild and severe cases(2, 6, 8, 14), there were no studies focused on neither the point-to-point nor the dynamic changes of these parameters in a period from admission to exacerbation so far. APACHE II scores, which reflects the overall disease severity, and SOFA scores, which reflects multiple organ dysfunction, were significantly increased on the day of exacerbation. Most commonly correlated clinical parameters with these two indices were NLR, serum level of lactic acid, LDH and albumin. NLR is a parameter used to evaluate the prognosis of severe patients with sepsis(15), and recently was suggested to bear potentials to predict the outcomes of COVID-19 patients with a cutoff value of 3.13 (16). In current cohort, not only a significant increment of NLR between admission and exacerbation stage, but also a sharp ascendant trend through entire para-exacerbation period was observed, which endorsing the reason to take this parameter as the promising index to predict the illness progression and should be continuously monitored in COVID-19 patients.

Data in current study echo the previous reports on the serum albumin and LDH, such as the report showed that the serum albumin level was decreased in 98% COVID-19 patients on admission(8), and another one showed that serum albumin level was lower and LDH level was higher in COVID-19 patients received ICU care than those did not received(14). In this study, data showed that once exacerbated, COVID-19 patients presented lower serum albumin and higher serum LDH, in comparison to the presences on hospital admission. Dynamic profile showed that the ascendance of LDH enlarged as early as 4 days before the exacerbations, and continuously being so until the day of exacerbation. Notably, the increase in LDH was not compatible with the changes in other liver enzymes, such as aspartate aminotransferase and alanine aminotransferase, which were basically remain unchanged in para-exacerbation period. Thus, the abundant LDH might source from lymphocytes or cardiocytes, etc., other than hepatic cells. For serum albumin, it was slightly but continuously decreased from 4 days in advance till the day of exacerbation, which may indicate the involvements of worsened malnutrition in COVID-19 patients that undergoing disease progression, necessitating the nutrition supplemental therapy in the treatment of even mild COVID-19 patients.

Plasma lactic acid is often influenced by the microcirculation perfusion and tissue oxygen saturation. In current study, lactic acid was measured in both the vein blood and the artery blood samples. However, the changes of lactic acid were more prominent in vein than in artery samples. In this group of patients, lactic acid concentrations in vein started to increase 4 days in advance to their exacerbations and then remained the high level afterwards. This observation may indicate that microcirculation dysfunction has involvements in the disease progression and multiple organ injury. Consistently, using of high dose of vitamin C to cure the abnormal microcirculation is recommended in an expert consensus for the treatment of severe COVID-19 patients(13).

Lymphocytopenia has been recognized as the most typical clinical characteristics of COVID-19 patients since the very beginning of the disease outbreak(8, 14). In a recent 1099 patients cohort, 80.4% nonsevere patients and 96.1% severe patients with COVID-19 had lymphocyte count lower than $1.5 \times 10^9/L$ (2). Besides the different incidence, the extent of lymphocytopenia was also more serious in severe COVID-19 patients than those in mild ones(6, 14). Current study firstly demonstrated that differentiated lymphocytes, including CD3, CD4 and CD8, were universally decreased at the day of admission. Secondly, this study further demonstrated that the population of lymphocytes would shrink further in a patient from the day of admission to the day of exacerbation and this descendancy can be traced as early as four days in advance to exacerbations, suggesting vigilance should be arisen if lymphocytopenia continuously worsening.

It is of note to address the increase of fibrinogen in COVID-19 patients, for it has been previously reported to be a driver for kidney and muscle fibrosis(17, 18), and involved in the pulmonary fibrosis at the very early acute inflammation stage in mice(19). Given pathological examinations revealed an extensive presence of massive pulmonary interstitial fibrosis in the lung of a severe patient(12), whether the increased serum fibrinogen is a sign to indicate the formation of the lung interstitial fibrosis needs further explorations.

This study has several limitations. First, patients were recruited from single center and the sample size was small. It would be better to include as many patients as possible in other cities in China, and even in other countries to get a more comprehensive understanding of the exacerbation process of COVID-19 patients. Second, the viral load was not continuously monitored and serum cytokines were not tested at the early stage of these patients. These two parameters are both potentially useful for better understanding of disease developments and should be determined in further studies.

Conclusions

Patients with severe illness of COVID-19 have higher mortality rate and more vigilance should be given to prevent the occurrence of exacerbations. Continuously monitoring crucial clinical parameters, such as NLR, serum albumin, LDH, lactic acid, *etc.* will be helpful to improve the recognition of the disease progression in patients with COVID-19 at early stage.

Abbreviations

SRAS-CoV: Severe Acute Respiratory Syndrome-Coronavirus

WHO: World Health Organization

COVID-19: Coronavirus Disease 2019

ICU: intensive care unit

IQR: interquartile range

RT-PCR: Reverse Transcription-Polymerase Chain Reaction

CT: computed tomographic

GGO: ground-glass opacity

GCS: Glasgow Coma Scale

SOFA: Sequential Organ Failure Assessment

APACHE II: Acute Physiology and Chronic Health Evaluation II

PFR: PaO₂ to FiO₂ rate

A-aDO₂: alveolar-arterial PO₂ difference

ECMO: extracorporeal membrane oxygenation

NLR: neutrophil to lymphocyte ratio

WBC: white blood cell

FDP: fibrinogen degradation product

LDH: lactate dehydrogenase

CD: cluster of differentiation

Declarations

Ethics approval and consent to participate

This retrospective study has been approved by the Shanghai Public Health Clinical Center Ethics Committee (No. YJ-2020-S015-01) and exempted from the need for written informed consent from patients for emerging infectious disease.

Consent for publication

Not applicable

Availability of data and material

The datasets analysed during the current study are available from the corresponding author on reasonable request.

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Competing interests

All authors declare no competing interests.

Author contributions

1. B collected, processed and summarized the epidemiological and clinical data, drafted the manuscript. Y. Z, Y. L, L. Q and F. D collected and processed the epidemiological and clinical data. H. L summarized and explained the data, revised the final manuscript. M. Z summarized and explained

the data, drafted and revised the final manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Clinical characteristics of study patients

Characteristics	median/n	%/IQR
Demographics		
male	18	81.8
female	4	18.2
age (yr.)	67	63-79
Comorbidities		
	6	27.3
without comorbidities	14	63.6
Hypertension	10	45.5
cardiovascular disease	6	27.3
diabetes	3	13.6
mental disorders	1	4.5
malignancy	1	4.5
hypothyroidism	1	4.5
chronic kidney disease	22	100.0
Symptoms on hospital admission		
fever	7	31.8
dry cough	6	27.3
expectoration	6	27.3
short breath	4	18.2
chest tightness	3	13.6
shiver	3	13.6
fatigue	3	13.6
myalgia	2	9.1
pharyngalgia	2	9.1
hemoptysis	22	100.0
diarrhea	10	45.5
dyspnea	6	27.3
Worsened symptoms on exacerbations		

	exaggerated fever	4	2-8
	abnormal consciousness	10	4-11
	cerebral infarction	14	13-15
Clinical durations		4	2-7
	ill onset to hospital admission	11	6-12
	ill onset to the 1st exacerbation	8	36.4
	ill onset to the 2nd exacerbation	10	45.5
	hospital admission to the 1st exacerbation	4	18.2
	hospital admission to the 2nd exacerbation	13	59.1
Oxygen supports after the first exacerbation			4
	Hi-flow oxygen therapy	11	50.0
	intubation +MV	7	31.8
	ECMO+ intubation +MV	8	36.4
Treatments after admission			18
	glucosteroids	12	54.5
	no antiviral	9	40.9
	one antiviral drug	4	18.2
	two combined antiviral drugs	4	18.2
	Thymopeptide	18	81.8
	Human Immunoglobulin injection	4	18.2
	antibiotics	67	63-79
	Human albumin injection	6	27.3
	low molecular weight heparin	14	63.6
	Chineses traditional medicine	10	45.5
Differential lymphocyte count on admission (cells/ul)			
	CD3 (normal range:690-2540)	266.5	116-558.8
	CD4 (normal range: 410-1590)	141.0	75-282
	CD8 (normal range: 190-1140)	122.0	29-284

Table 2. Comparisons of clinical characteristics between para-exacerbation period

	admission		exacerbation		difference
	media/n	IQR/%	media/n	IQR/%	p
Vital signs					
temperature	37.5	36.8-38.4	38.1	37.0-39.1	0.258
<38	12	60	18	69.2	
38-39	3	15	3	11.5	0.225
>39	5	25	5	19.2	
blood pressure	96.0	86.2-103.9	90.0	77.3-95.2	0.235
≥100	10	50	8	30.8	0.234
<100	10	50	20	76.9	
heart rate	93.5	79.8-102.3	90.0	81-111.3	0.830
≥100	6	30	8	30.8	1.000
<100	14	70	18	69.2	
respiratory rate	21.0	18.8-22.3	31.5	23-35.3	0.002
<20	9	45	4	15.4	
20-30	11	55	9	34.6	0.015
>30	0	0	13	50.0	
Laboratory findings					
WBC (10 ⁹ /L)	4.3	3.5-6.6	8.1	6.5-10.4	0.003
>9.5	0	0	13	50.0	
3.50-9.50	16	80	11	42.3	0.012
<3.5	4	20	2	7.7	
Neutrophil (10 ⁹ /L)	3.3	2.4-5.1	7.4	5.6-9.4	0.003
≤6.3	16	80	6	23.1	0.014
>6.3	4	20	20	76.9	
Lymphocytes (10 ⁹ /L)	0.8	0.5-1	0.5	0.3-0.6	0.012

>1.1	4	20	0	0.0	
1.1~0.5	8	40	15	57.7	0.225
<0.5	8	40	9	34.6	
neutrophil/lymphocyte ratio	5.62	2.6-8.6	15.39	8.1-23.2	0.002
CRP (mg/L)	278.0	21.4-83.8	176.0	53.3-96.3	0.267
<20	4	20	0	0.0	0.191
20-100	14	70	18	69.2	
>100	2	10	8	30.8	
Procalcitonin (ng/ml)	133.5	0.1-0.6	58.5	0.1-0.8	0.239
0.01-0.1	8	40	4	15.4	
0.5-1	10	50	16	61.5	0.157
>1	2	10	6	23.1	
ESR (mm/H)	84.0	40.8-103.3	86.0	52-119.3	0.504
<50	8	40	5	19.2	
50-100	8	40	8	30.8	0.318
>100	4	20	13	50.0	
fibrinogen (g/L)	4.7	3.8-5.8	6.5	5.8-7.5	0.002
≤5	10	50	6	23.1	0.189
>5	10	50	20	76.9	
FDP (ug/ml)	1.5	1-3.1	3.4	2.6-7.2	0.012
≤5	18	90	11	42.3	0.037
>5	2	10	15	57.7	
d-dimer (ug/ml)	0.6	0.4-1	1.5	0.9-2.4	0.026
≤1	16	80	5	19.2	
1~3	4	20	13	50.0	0.008
>3	0	0	8	30.8	
PaCO2 (mmHg)	37.6	25.2-42.9	35.3	24.6-40.4	0.239
≤32	0	0	8	30.8	

32-45	18	90	13	50.0	0.100
>45	2	10	5	19.2	
PaO2/FiO2 ratio (mmHg)	315.2	178.5-446.5	68.5	64.1-95.2	0.001
>300	10	50	0	0.0	
100-300	10	50	6	23.1	0.000
<100	0	0	20	76.9	
artery lactic acid (mmol/L)	1.7	1.5-2.5	2.5	1.6-3.9	0.225
<2	12	60	10	38.5	0.688
≥2	8	40	16	61.5	
vein lactic acid (mmol/L)	2.6	2.2-3.2	3.8	3.3-4	0.004
≤3	12	60	9	34.6	0.046
>3	8	40	17	65.4	
Aspartate aminotransferase (U/L)	24.0	12.8-30.3	28.0	19.3-43	0.061
≤50	18	90	22	84.6	1.000
>50	2	10	4	15.4	
Alanine aminotransferase (U/L)	31.0	25.5-52.8	49.5	28-57.5	0.086
≤50	14	70	17	65.4	1.000
>50	6	30	9	34.6	
Lactate dehydrogenase(U/L)	320.5	252.8-412.8	516.5	422-605	0.012
≤368	14	70	4	15.4	0.009
>368	6	30	22	84.6	
Albumin (g/L)	38.9	37.7-39.8	32.5	30.6-35.7	0.002
≥35	18	90	5	19.2	0.001
<35	2	10	21	80.8	
prealbumin (mg/L)	103.2	68.7-120.5	79.6	41.7-101.5	0.123
100-180	12	60	5	19.2	0.046

<100	8	40	21	80.8	
pH	7.4	7.4-7.4	7.4	7.4-7.5	0.483
<7.35	2	10	5	19.2	
7.35-7.45	16	80	13	50.0	0.438
>7.45	2	10	8	30.8	
Potassium (mmol/L)	3.9	3.3-4	3.7	3.5-3.8	0.873
<3.5	6	30	5	19.2	0.644
3.5-5.3	14	70	21	80.8	
Sodium (mmol/L)	137.5	132.8-139.3	138.0	134.5-140.5	0.468
<137	8	40	10	38.5	1.000
137-147	12	60	16	61.5	
Creatinine (mmol/L)	80.2	56.4-96.8	74.2	57.1-112.9	0.786
<57	4	20	5	19.2	
57-111	12	60	13	50.0	0.868
>111	4	20	8	30.8	
Hematocrit (%)	38.1	34.3-42	38.7	30.6-39.7	0.039
≤40	10	50	20	76.9	0.234
>40	10	50	6	23.1	
Hypersensitive troponin I (ng/ml)	0.1	0-0.1	0.1	0-0.1	0.882
<0.04	11	55	5	19.2	
>0.04-0.1	6	30	16	61.5	0.462
>0.1	3	15	5	19.2	
Myoglobin (ng/ml)	64.3	19.3-206.9	54.2	29.7-164	0.378
≤48	8	40	11	42.3	1.000
>48	12	60	15	57.7	
proBNP (pg/ml)	76.2	34.7-644.3	465.1	139-1376	0.028
≤250	16	80	11	42.3	0.109

>250	4	20	15	57.7	
Platelet count (10 ⁹ /L)	152.0	127.8-202.5	162.5	119.5-229	0.417
≤125	4	20	7	26.9	1.000
>125	16	80	19	73.1	
Total bilirubin (μmol/L)	13.2	8.5-19.1	8.6	6.9-15.8	0.256
≤20.5	18	180	19	73.1	0.617
>20.5	2	20	7	26.9	
AaDO ₂ (mmHg)	100.0	39.9-168	494.4	335-534	0.000
GCS	15.0	15-15	15.0	12.8-15	0.107
APACHE II	6.0	3.8-8	31.0	29-34.8	0.000
SOFA	2.5	1-4	5.5	4-7	0.004
Radiological findings					
Lung segments involved	14.0	10-16	19.0	18-19	0.013
Total image score	14.0	12-21	31.0	30-37	0.004
Ventral lung image score	8.0	5-12	15.0	14-21	0.004
Dorsal lung image score	8.0	6-10	19.0	16-26	0.009
Ground-glass opacity	18	100.00	18	100.00	1.000
Local consolidation of lung	2	11.11	18	100.00	0.061
Peripheral bronchiectasis	6	33.33	18	100.00	1.000
Fiber stripe opacities	6	33.33	10	55.56	1.000
Interlobular septal thickening	2	11.11	4	22.22	0.455
Visceral pleura involved	18	100.00	18	100.00	1.000
Interlobar fissure thickening	6	33.33	14	77.78	0.242
Peripheral small pulmonary artery thickening	18	100.00	18	100.00	1.000
WBC: whole blood cell, FDP: fibrinogen degradation product, CRP: C-reactive protein, BNP: brain natriuretic peptide, A-aDO ₂ : alveolar-arterial PO ₂ difference, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, GCS: Glasgow Coma Scale					

Figures

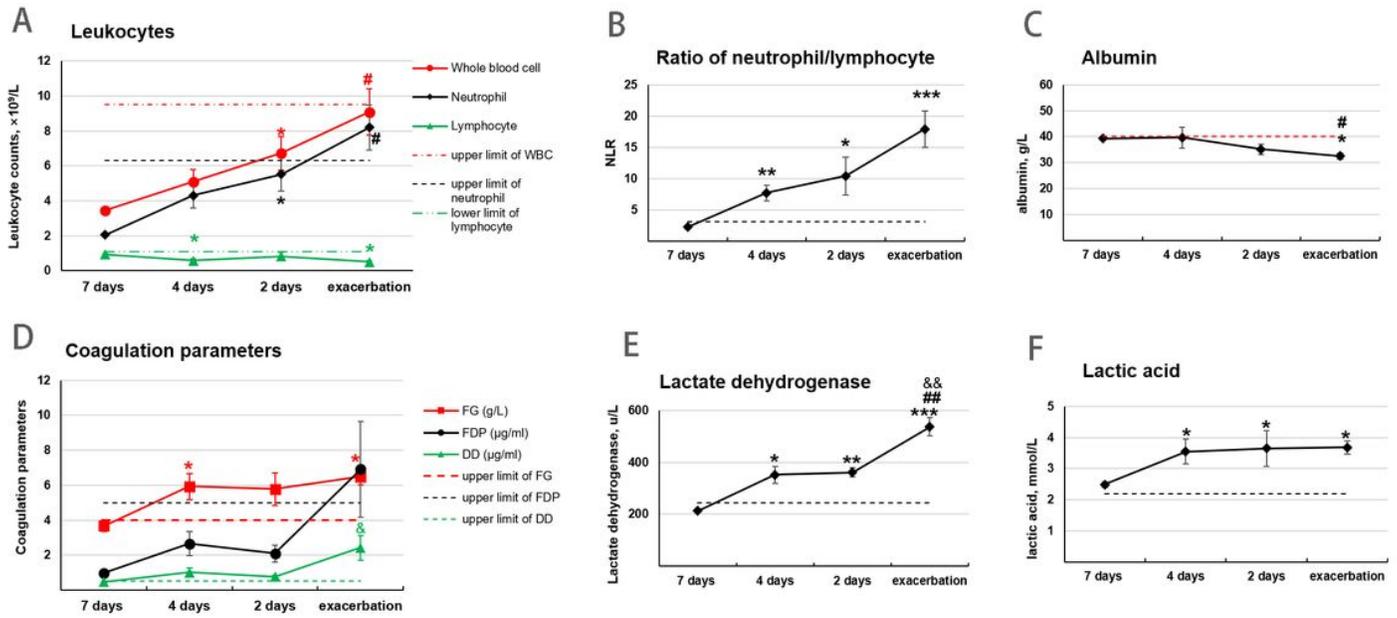


Figure 1

Timeline charts illustrate the laboratory parameters in patients with COVID-19 at different intervals from the day of exacerbation. The number of patients in each group of data were: 4 in 7 days, 11 in 4days, 16 in 2 days, and 22 in exacerbation day. The dotted lines in black show the lower normal limit of each parameter, and the dotted line in red shows the upper normal limit of serum albumin concentration. * \square $p < 0.05$, ** \square $p < 0.01$, *** \square $p < 0.001$, compared with data of 7 days; # \square $p < 0.05$, ## \square $p < 0.01$, ### \square $p < 0.001$, compared with data of 4 days; && \square $p < 0.01$, compared with data of 2 days.

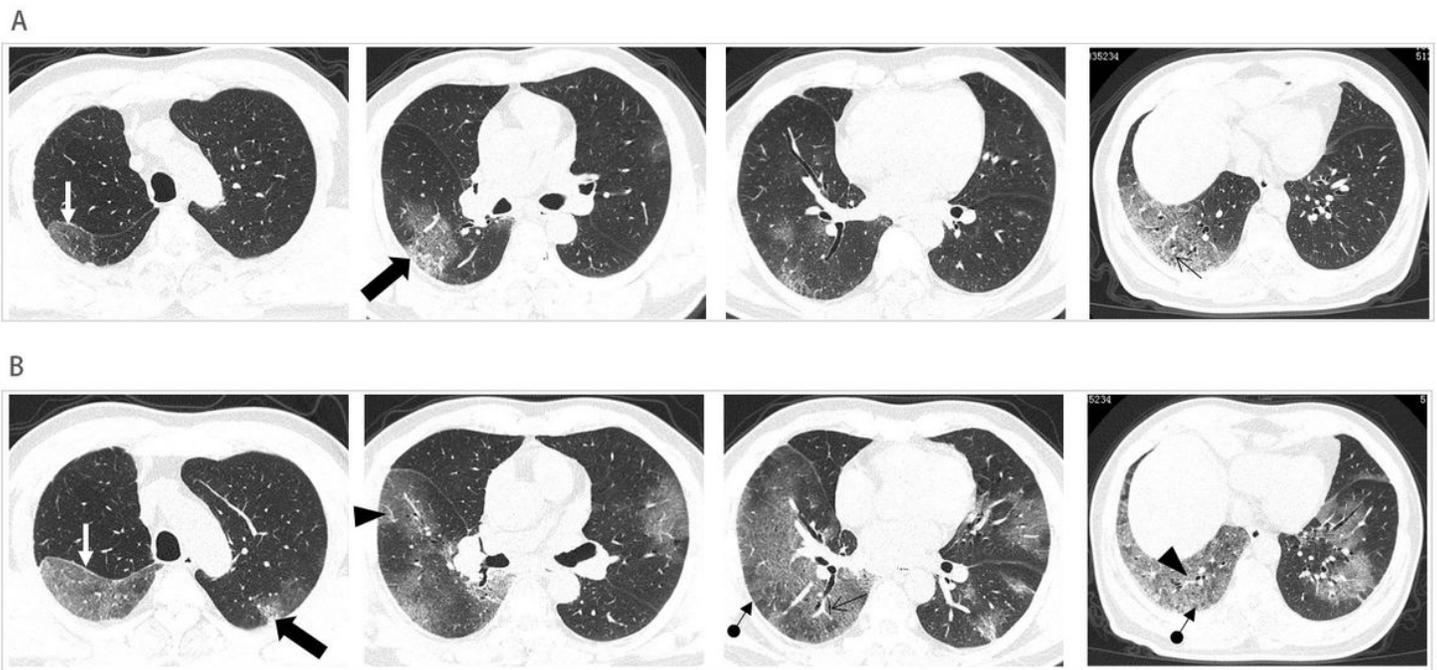


Figure 2

CT images were from a 65 male COVID-19 patient with a symptom onset on Jan 26, 2020. A: Images on Feb 2, 2020, the day of hospital admission. B: Images on Feb 5, 2020, the day of exacerbation. White arrow indicates visceral pleura involvement, black arrowhead indicates peripheral bronchiectasis, arrowhead with tail tip indicates interlobular septal thickening, direction arrow shows the local lung consolidation and visceral pleura involvement, triangle indicates peripheral small pulmonary artery thickening.