# Analyses of the clinical features and contributing factors in 13 fatal cases of Coronavirus Disease 2019

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# SUBJECT AREAS

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# **KEYWORDS**

Coronavirus Disease 2019, Death, Clinical analysis

# Abstract

Objective To investigate the clinical features of and contributing factors in 13 fatal cases of Coronavirus Disease 2019 (COVID-19).

Methods The clinical data of 13 patients who died of COVID-19 in Central Theater General hospital, China, between January 4, 2020, and February 24, 2020, were analyzed retrospectively. The data reviewed included clinical manifestations, laboratory test results and radiographic features. The cellular immune function and the expression of inflammatory factors in deceased patients at different stages of the disease were analyzed, and the clinical data and laboratory test results between the deceased group and the moderate group (20 patients), severe group (20 patients) and the critical group (10 patients) were compared.

Results Of those who died, the patients consisted of 10 men and 3 women. The average age of those who died was  $(74\pm19)$  years, and 10 patients were over 70 years old (76.9%), which was significantly higher than the ages of patients in the moderate group, severe group and critical group. There were no significant differences in sex ratio and clinical manifestations among the 4 groups. For the patients who died, 9presented with underlying diseases,6 of whom had more than 2 diseases, which was significantly higher than the number of underlying disease in the other groups. On admission, the chest computed tomography (CT) for 8 patients (61.5%) mainly showed multiple patchy ground-glass opacities. When the disease progressed, the ground-glass opacities rapidly developed into diffuse lesions in both lungs. The lymphocyte and CD3 + ,CD4 + , and CD8 + T lymphocyte counts in the peripheral blood of 13 patients were significantly lower than normal levels and decreased more substantially during the disease course based on the levels when admitted (P<0.01). Additionally, the IL-6, D-dimer, C-reactive protein (CRP), lactic acid levels gradually increased, and most peaked before death. There were statistically significant differences in IL-6 expression, lymphocyte count and T lymphocyte subset count between the deceased group and the moderate group, severe group and critical group (P<0.01). However, there were no statistically significant differences in serum CRP lactic acid levels among the 4 groups (P>0.05). The cause of death for most patients was acute respiratory distress syndrome (ARDS) with type I respiratory failure. Three patients eventually developed

multiorgan deficiency syndrome (MODS).

Conclusion The risk factors of death for COVID-19 patients included older men, more underlying diseases, poor cellular immune function and overexpression of inflammatory factors. The main cause of death in patients with COVID-19 was ARDS, which led to respiratory failure and MODS.

#### 1 Background

December 2019 marked the beginning of the coronavirus disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) in Wuhan, Hubei. Because it is highly contagious and the entire population is susceptible <sup>[1-2]</sup>, the disease spread rapidly nationwide and throughout many other countries <sup>[3-4]</sup>, causing worldwide concern. The priority task is enhancing the cure rate and reducing mortality. From January 4, 2020, to February 24, 2020, a total of 339 patients were admitted to our hospital, of whom 13 died. The clinical features, laboratory test results and causes of death related to these 13 fatal cases are summarized here in.

#### 2 Methods

# 2.1 Subjects

The data for 13 fatal cases of COVID-19 involving patients admitted to our hospital from January 4, 2020, to February 24, 2020, were collected. Another 20patients with moderate, 20 patients with severe COVID-19 and 10 patients with critical COVID-19 who were admitted during the same period were enrolled as the control group. All confirmed patients were graded per the Diagnosis and Treatment Protocol for COVID-19 (Pilot 6th Edition)<sup>[5]</sup> issued by the National Health Commission. Moderate cases were defined as patients who had fever, respiratory tract symptoms, and imaging-confirmed pneumonia. Severe cases were defined as patients who met one of the following conditions: respiratory distress, RR  $\geq$  30 times/min; oxygen saturation  $\leq$  93% at rest; PaO<sub>2</sub>/FiO<sub>2</sub> < 300 mmHg (1 mmHg = 0.133 kPa); and > 50% apparent progress of the lesions within 24-48 h confirmed by chest imaging. Critical cases were defined as patients who met one of the following conditions: onset of respiratory failure requiring mechanical ventilation; onset of shock; and concurrent with other organ failure, requiring ICU care.

#### 2.2 Methods

General information, underlying diseases, and clinical and imaging manifestations were collected for

the deceased patients. The laboratory examination results (routine blood examination, lymphocyte subtypes, blood coagulation analysis, and inflammatory factor levels) at various stages of the disease course (on admission, in progress and before death) were collected for the deceased patients and analyzed. Additionally, the clinical and laboratory test data were collected form oderate, severe, and critical patients for comparisons. All laboratory examinations and imaging scans were repeated at an average interval of 1–3 days and 3–5 days, respectively.

### 2.3 Statistical analysis

Using SPSS 23.0, data with a normal distribution are expressed as the mean  $\pm$  SD. ANOVA was used for multiple comparisons, and the LSD-t test was used for further pairwise comparisons. Numerical data are expressed as % and were compared using the chi-square test. The significance level was set

at P < 0.05.

3 Results

3.1 General clinical data

The 13 fatal cases involved 10 males (76.9%) and 3 females with an average age of 31–96 (74  $\pm$  19), which was significantly higher than that of patients with moderate and critical disease. Ten patients (76.9%) in the deceased group were > 70 years old, significantly older than patients in the other 3 groups (P < 0.01). No statistically significant difference in the gender ratio and clinical manifestations was seen among the 4 groups. Nine out of 13 fatal cases involved concurrent underlying diseases, among which 7 involved hypertension (53.8%), 3 involved coronary heart disease (23.0%), 2 involved advanced cancer, 2 involved hypothyroidism, 2 involved cerebral infarction, 1 involved type II diabetes mellitus, 1 involved chronic bronchitis, and 1 involved sicca syndrome. In addition, 6 patients (46.1%) in the deceased group presented with more than 2 concurrent underlying diseases, significantly more than that presented by patients in the other 3 groups (P < 0.01; Table 1). Table 1. Group comparison of clinical data

Index	Moderate	Severe	Critical	Fatal
	(n=20)	(n=20)	(n=10)	(n=13)
Age(year, x±s)	46±18	60±16	52±10	74±19 <sup>ac</sup>
≥70 years old (n,%)	5(25.0)	6(30.0)	1(10.0)	10(76.9) <sup>at</sup>
Sex(n, male/female)	14/6	14/6	8/2	10/3
Clinical manifestations (n,%)				
Fever	17(85.0)	18(90.0)	10(100)	11(84.6)
Cough	14(70.0)	15(75.0)	7(70.0)	8(61.5)
Fatigue	8(40.0)	10(50.0)	5(50.0)	6(46.1)
Chest distress and polypnoea	1(5.0)	2(10.0)	2(20.0)	3(23.0)
Diarrhea	3(15.0)	4(20.0)	2(20.0)	2(15.3)
Underlying disease (n,%)				
Hypertension	7(35.0)	11(55.0)	5(50.0)	7(53.8)
Coronary heart disease	3(15.0)	4(20.0)	1(10.0)	3(23.0)
Type II diabetes mellitus	2(10.0)	4(20.0)	1(10.0)	1(7.6)
Other diseases	1(5.0)	3(15.0)	2(10.0)	8(61.5) <sup>ab</sup>
Over 2 underlying diseases	1(5.0)	2(10.0)	1(10.0)	6(46.1) <sup>ab</sup>

<sup>a</sup>compared with moderate cases, P<0.01; <sup>b</sup>compared with severe cases, P<0.01; <sup>c</sup>compared with

critical cases, P<0.01

# 3.2 Chest CT

On admission, the 13 patients in the deceased group presented abnormal chest CT findings, among whom 8 patients presented multiple patchy or small patchy ground-glassopacities (61.5%), 2 patients

presented scattered thin ground-glass opacities in both lungs (15.3%), 1 presented a single groundglass opacity (7.6%), 1 presented 2 unilateral focal lesions (7.6%), and 1 presented subpleural large patchy high-density shadows in both lungs (7.6%) (Fig. 1). Except for 1 patient who died on the day of admission, the remaining patients showed disease progression to different extents by chest CT and were retested after 3–6 days; the characteristics of the imaging findings included enlargement of patchy ground-glass opacities and the emergence of patchy shadows in other lung fields with partial consolidation. The formation of diffuse lesions in both lungs occurred within (9 ± 3) days (Fig. 2). 3.3 Comparison of absolute peripheral blood lymphocyte counts and T lymphocyte subset counts among deceased patients by disease course As shown in Table 2, in the 13 patients, the absolute peripheral blood lymphocyte counts and CD3<sup>+</sup>, CD4<sup>+</sup>, andCD8<sup>+</sup>T lymphocyte counts were lower than the normal values on admission and further decreased, reaching the lowest levels as the disease progressed and before death. A significant

difference in the above parameters was observed among the disease-progression set, before-death set, and on-admission set (P < 0.01).

Table 2 Comparison of absolute peripheral blood lymphocyte counts and T lymphocyte

Disease course	Lymphocytes	CD3 <sup>+</sup>	CD4 <sup>+</sup>	CD8 <sup>+</sup>
	(×10 <sup>9</sup> /L)	(counts/µl)	(counts/µl)	(counts/µl)
On admission	0.45±0.23	360±28	198±17	168±3
				2
Progression	0.33±0.18*	261±17*	120±95*	126±2
				8*
Before death	$0.18 \pm 0.06^{*\#}$	165±53* <sup>#</sup>	66±67* <sup>#</sup>	91±44*
				#

subset counts by disease course

Compared with the on-admission data set, \*P<0.01; compared with disease -progression data set,

# <sup>#</sup>P<0.01

# 3.4 Comparison of inflammatory factor and lactic acid levels among the deceased patients by disease course

On admission, the 13 patients who eventually died presented normal D-dimer levels and high IL-6, CRP, and lactic acid levels. As the disease progressed, the indicators increased further and peaked before death. Significant differences in the above parameters were observed between the disease-progression set and on-admission set and between the before-death set and on-admission set(P < 0.01, Table 3).

Table 3.	Comparison	of inflammatory	factor and	lactic acid	levels by	disease course

Disease course	D- dimer	IL-6	CRP	Lactic acid
	(ng/ml)	□pg/ml□	[]mg/L[]	(mmol/L)
On admission	207±130	56.3±6.9	33.6±10.7	1.9±0.3
Progression	1309±472*	114.5±37.2*	86.1±55.8*	3.3±0.7*
Before death	4226±536* <sup>#</sup>	166.3±40.5* <sup>#</sup>	125.2±67.4* <sup>#</sup>	5.1±0.4* <sup>#</sup>

Compared with on-admission data set, \*P<0.01; compared with disease -progression data set,

# <sup>#</sup>P<0.01

3.5 Comparison of absolute peripheral blood lymphocyte counts and T lymphocyte subset counts and D- dimer, IL-6, CRP, and lactic acid levels among different groups on admission On admission, the absolute peripheral blood lymphocyte counts and T lymphocyte subset counts in the 13 patients were significantly lower than those in patients in the moderate, severe, and critical groups and became lower as the disease progressed (P < 0.01). All patients showed normal D-dimer levels on admission. The serum IL-6 level in the deceased group was significantly higher (P < 0.01) than those in the other 3 groups, in the following descending order: critical group, severe group and moderate group. No significant differences were observed for CRP and lactic acid levels between the death group and the other 3 groups (P > 0.05, Tables 4 and 5).

Table 4.Comparison of absolute peripheral blood lymphocyte counts and T lymphocyte subset counts

Groups	Lymphocytes	CD3 <sup>+</sup>	CD4 <sup>+</sup>	CD8 <sup>+</sup>
	(×10 <sup>9</sup> /L)	(counts/µl)	(counts/µl)	(counts/µl)
Moderate(n=20)	0.97±0.28	712±45	445±35	306±38
Severe(n=20)	0.75±0.11	583±37	358±27	233±35
Critical(n=10)	0.58±0.19	410±14	285±14	196±13
Deceased(n=13)	0.45±0.23	360±28	198±17	168±32
F value	8.23	124.21	103.74	21.10
P value	<0.01	< 0.01	<0.01	<0.01

by group (mean  $\pm$  SD)

Table 5.Comparison of inflammatory factor and lactic acid levels by group (mean±SD)

Groups	D- dimer	IL-6	CRP	lactic acid
	(ng/ml)	(pg/ml)	(mg/L)	(mmol/L)
Moderate(n=20)	173±114	7.6±1.7	27.7±9.	$1.5 \pm 0.5$
			5	
Severe(n=20)	185±127	24.1±6.1	28.5±1	1.5±0.2
			1.4	
Critical(n=10)	214±119	36.3±2.9	30.4±1	1.6±0.7
			2.3	
Deceased(n=13)	207±130	56.3±6.9	33.6±1	1.9±0.3
			0.7	
F value	104.1	82.6	76.5	9.58
P value	0.24	<0.01	0.20	0.16

# 3.6 Clinical treatments

All the patients received antiviral treatment on the basis of symptomatic treatments, which primarily included interferon $\alpha$  inhalation (5 million units, bid, 5–7 d), ribavirin intravenous injection (0.5 g, bid, 5–7 d), oral oseltamivir phosphate capsules (75 mg, bid, 5–7d), arbidol hydrochloride (0.2 g, tid, 5–14 d) or lopinavir/ritonavir tablets(500 mg, bid, 5–7 d). All the patients received antibiotics, mainly including fluoroquinolones and  $\beta$ -lactams, etc. Twelve patients received 5% human immumoglobulin (intravenous injection), 9 patients received thymosin  $\alpha$ 1 (subcutaneous injection), 9 patients received 25% human albumin(intravenous injection), 12patients received methylprednisolone (40 mg or 80 mg, intravenous injection, bid, 5–7 d), 10 received mechanical ventilation, and 1 underwent ECMO therapy.

# 3.7 Causes of death

Among the 13 patients who died, 1 died of sudden cardiac death caused by hypoxia, and the others

died of type I respiratory failure caused by serious ARDS, with 4 patients having type II respiratory failure, 3having multiple organ dysfunction syndrome (MODS), 2having heart rhythm disorders (ventricular fibrillation), and 1having septic shock.

#### 4 Discussion

SARS-CoV-2 and SARS-CoV are from the same species. To date, the prevalence rate and the deaths caused by COVID-19 have far exceeded those caused by SARS (severe acute respiratory syndrome) in 2003. As of 24:00 February 24, 2020, in China, there were77,658 cumulative confirmed COVID-19 cases, with 27,323 cured and 2,663 deaths <sup>[6]</sup>, for a mortality rate of approximately 3.4%. Ten of the 13 patients (76.9%) who died were male, which was consistent with the results described in previous studies<sup>[7-10]</sup>. The average age of the deceased group was  $74 \pm 19$ , with 10 patients older than 70 years old (76.9%), higher than the ages of the patients in the moderate, severe, and critical groups. In the critical group, only 1 patient was older than 70 years (10.0%), indicating that the survival probability in patients older than 70 years old is very low once the disease progresses into the critical stage. No significant differences in clinical features were seen between the deceased group and the other 3 groups on admission, with primary symptoms of fever, fatigue and dry cough, as well as nausea, vomiting, abdominal pain and diarrhea observed in few patients, which is consistent with previous studies [11-12], indicating that patients with severe disease are rarely identified only by clinical manifestations at the early stage. Ten of the 13 patients who died had underlying diseases, with hypertension (53%) and coronary heart disease (23%) being the most common. Consistent with our study results, several previous studies showed that approximately 57.5% of patients with COVID-19 had at least 1 underlying disease, including hypertension, diabetes mellitus and/or cardiovascular disorders. Among them, the patients with underlying hypertension and heart disease were susceptible to progression into critical condition [13-15]. In our study, 6 patients in the deceased group had more than 2 underlying diseases (46.1%), significantly higher than that in the other 3 groups, indicating that COVID-19 patients with multiple chronic underlying diseases are at a higher risk of death.

On admission, the 13 patients all presented abnormal chest CT findings, with 8 (61.5%) exhibiting multiple patchy ground-glass opacities in both lungs, indicating that the wider the lesion area during the early state, the more possible a respiratory failure will occur with progression, which should draw clinical physicians' attention. Notably, 4 out of the 13 patients who eventually died showed nonserious chest imaging abnormalities on admission characterized as a single ground-glass opacity, focal lesion or scattered thin ground-glass opacities in both lungs. However, repeated chest CT on days 3-6 after admission showed apparent progression characterized as an increase in ground-glass opacities and the emergence of patchy shadows with partial consolidation, progressing into diffuse lesions in both lungs on day9  $\pm$  3 (mean) after admission, indicating that this disease progresses rapidly and that frequently repeated chest CT exams at the early stage are necessary. As an essential part of the human immune system, cellular immune function plays a critical role in fighting viral infections by regulating and maintaining the ratio of T lymphocyte subsets. A study showed that 83.2% of COVID-19 patients presented lymphopenia on admission [16]. In a retrospective analysis of clinical data of COVID-19 patients, Guo et al.<sup>[15]</sup> showed that compared with the survival group, the deceased group had significantly decreased absolute counts of CD3<sup>+</sup>,CD4<sup>+</sup>, and CD8<sup>+</sup>T cells, indicating a correlation between cellular immune function and prognosis. In our study, the laboratory examination results showed that absolute peripheral blood lymphocyte counts and T lymphocyte subset counts in the deceased group at the early state were decreased and significantly lower than those in the other 3 groups, followed by a more substantial decrease as the disease progressed, with the lowest values obtained before death. One of the patients had an absolute lymphocyte count of  $0.06 \times 10^9$ /L before death. These results indicated that there is a relationship between the decrease in absolute peripheral blood lymphocyte counts and T lymphocytes subset counts as the severity increases. In addition, dynamic routine blood tests and T lymphocyte subset tests are predictors of disease progression and patient prognosis to a certain extent. Even though normal human immune function can eliminate foreign microbiological matter, control infections and restore the body, viruses can elicit abnormal excessive immune responses and induce

a substantial cytokine release by mononuclear macrophages and endothelial cells, thereby triggering a cytokine storm, resulting in serious injuries to organs and tissues <sup>[17]</sup>. Elevated serum levels of several inflammatory factors and C-reactive protein have been observed in COVID-19 patients, and the expression of inflammatory factors is related to disease severity<sup>[9, 18]</sup>. The pathological results show a large inflammatory cells count in organs and tissues throughout the whole body, indicating an apparent inflammatory response in COVID-19 patients <sup>[19]</sup>. In our study, IL-6, CRP, and D-dimer, the 3 commonly used inflammatory indicators in clinical practice, and lactic acid were selected for observation. Additionally, serum lactic acid, an important biochemical indicator of the body's response to cell hypoxia and hemoperfusion, was used as a predictive measure of disease severity and patient prognosis. Our study found that all the indicators other than D-dimer in the deceased group were increased on admission. With disease progression, the levels of various inflammatory factors and lactic acid further increased, with a significant difference compared with the data on admission, until they peaked before death. These results indicate that there is a close correlation between the persistent excessive release of inflammatory factors and COVID-19 occurrence and progression, while persistent increasing serum lactic acid indicates persistent unimproved poor hemoperfusion. We found that even though IL-6, CRP and serum lactic acid showed different levels of increase in each group on admission, serum IL-6 was significantly higher in the deceased group than in the other 3 groups, in the following descending order: the critical group, severe group and moderate group. CRP and serum lactic acid showed nonsignificant differences among the various groups, indicating that IL-6 might be a more sensitive indicator of disease severity than other inflammatory factors and that dynamic monitoring of IL-6, CRP, D-dimer and lactic acid levels might be more valuable in predicting patient prognosis.

# 5 Conclusions

In conclusion, the survival probability of male patients older than 70 years old with multiple underlying diseases was very low once the disease progressed into the critical stage. Patients with multiple lesions in both lungs indicated by imaging at the early stage were susceptible to progression into critical conditions, which should draw clinical physicians' attention. Despite mild imaging

manifestations at the early stage, frequently repeated chest CT scans based on clinical symptoms are necessary in order to utilizetimely treatment. During the early stage, the lower the absolute peripheral blood lymphocyte counts and T lymphocytes subset counts are and the higher IL-6 is, the higher the severity and the death risk are. Dynamic monitoring of the above indicators might be valuable for evaluating patient prognosis.

# Abbreviations

COVID-19: Coronavirus Disease 2019;CT :Chest computed tomography; CRP:C-reactive protein; ARDS: Acute respiratory distress syndrome; MODS: Multiorgan deficiency syndrome; SARS: Severe acute respiratory syndrome syndrome; IL-6:Interleukin-6; ECMO: Extracorporeal membrane oxygenation Declarations

# Ethics approval and consent to participate

This study was approved by the Coordinating Ethics Committee of General Hospital of Chinese PLA Central Theatre Command (No. 2020-016).

# **Consent for publication**

Not applicable.

# Availability of data and material

All data generated or analyzed during the present study are included in this published article.

### **Competing interests**

The authors declare that there are no conflicts of interest.

### Funding

Not applicable.

# **Authors' contributions**

HL\_QS and ZH participated in the design of the study. LL and RX collected the data.CM and HL carried out the statistical analysis. HL and FZ drafted the manuscript. QS revised the manuscript. All authors read and approved the final manuscript.

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  Figures





Chest CT of the patient who died on the day of admission. A. multiple patchy ground-glass opacities in both lungs; B. scattered thin ground-glass opacities in both lungs; C. single ground-glass opacity; D. 2 unilateral focal lesions; E. large patchy high-density shadows in

both lungs



2020.1.31

2020.2.04

2020.2.09

#### Figure 2

Chest CT of a 67-year-old male in the deceased group. A. Chest CT on admission (January 31,2020): thin ground-glass opacities present in the anterior and posterior segments of the left superior lobe and the posterior segment of the right superior lobe; B. Day 4 after admission: enlargement of ground-glass opacities in both lungs on chest CT; C. Day 9 after admission: increase in lesions with consolidation present on chest CT and progression into diffuse ground-glass opacities in both lungs.