COVID-19 with Different Severity: A Multi-center Study of Clinical Features

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Author's Contribution

YF, YL, TB, JH, WX, DY, RC, FL, YL, XL, YC, XL, YL, HL, and JY collected the epidemiological and clinical data. SX, JL processed statistical data. YF and SX drafted the manuscript. JQ, HS, and ZL revised the final manuscript. ZL and JQ is responsible for summarizing all data related to the virus. MZ is responsible for summarizing all epidemiological and clinical data.

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At a Glance Commentary

Scientific Knowledge on the Subject

COVID-19 is posing an unprecedented threat to global health care systems. A number of observational studies have described clinical characteristics of COVID-19 patients in single centers. However, detailed clinical features of patients in different age groups with varying disease severities remain limited.

What This Study Adds to the Field

In our study, we found that adults with COVID-19 aged ≥75 years have poor outcomes and the in-hospital mortality rate of critical patients was 41.1%. Multiple pulmonary lobes involvement and pleural effusion were associated with a higher disease severity, while anti-hypertensive medication usage was not. These clinical features help clinicians to identify high-risk patients.

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Abstract

Rationale: COVID-19 pandemic is now a global health concern.

Objectives: We compared the clinical characteristics, laboratory examinations, CT images and treatment of COVID-19 patients from three different cities in China.

Methods: 476 patients were recruited from Jan 1 to Feb 15, 2020 at three hospitals in Wuhan, Shanghai and Anhui. Patients were divided into four groups according to age and into three groups (moderate, severe, and critical group) according to the fifth version of the guidelines issued by the National Health Commission of China on Diagnosis and Treatment of COVID-19.

Measurements and main results: Compared with moderate group (37.8%), the incidence of comorbidities was higher in severe (46.3%) and critical groups (67.1%). Compared with severe and critical groups, there were more patients taking ACEI/ARB in moderate group. More patients had multiple lung lobe involvement and pleural effusion in the critical group as compared to moderate group. Compared with the moderate group, more patients received antiviral agents within first 4 days than in severe group, and more patients received antibiotics and corticosteriods in critical and severe groups. Patients over 75 years old had significantly lower survival rate than the younger patients.

Conclusion: Multiple organ dysfunction and impaired immune function were the typical characteristics of severe and critical patients. There was a significant difference in angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers usage among patients with different severities. Involvement of multiple lung lobes and pleural effusion were associated

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with the severity of COVID-19. Advanced age (≥75 years) was a risk factor for mortality.

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Introduction

Corona Virus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has spread out in the world, posing a critical threat to global health. The novel betacoronavirus, an enveloped RNA virus, was first identified by high-throughput sequencing (1). SARS-CoV-2 has a similar receptor-binding domain structure to that of severe acute respiratory syndrome coronavirus (SARS-CoV) as shown by homology modelling (1). Zhou P *et al.* found that 96% of SARS-CoV-2 and bat coronavirus are similar at the whole-genome level (2). COVID-19 has been declared as a public health emergency by the World Health Organization. 571,678 laboratory-confirmed infections had been reported globally by March 29, 2020 (3).

Several studies have described the clinical characteristics and epidemiology of COVID-19 (1,3-6). These studies confirmed human-to-human transmission of COVID-19 and that SARS-CoV-2 infection could result in severe and even fatal acute respiratory distress syndrome. Three published reports on COVID-19 cases were from Wuhan, Hubei province (1,4,5). Two recent studies summarized the findings of a large number of laboratory-confirmed SARS-CoV-2 infections from 31 provinces/provincial municipalities (6,7). The Diagnosis and Treatment of COVID-19 guidelines (Fifth version) published by the National Health Commission of China was issued on February 8, 2020. These guidelines classified SARS-CoV-2 infections into four groups (mild type, moderate type, severe type, and critical type). Herein we compare the difference in clinical features, laboratory examinations, CT images and therapies including antiviral, antibacterial, antifungal agents, corticosteriods and antihypertensive medications use among three of the four groups (moderate type, severe type and critical type) and four age

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groups of 476 COVID-19 cases from three cities including Shanghai, Wuhan in Hubei Province and Tongling in Anhui Province. We also summarized the dynamic changes in CT images of improved patients to characterize the evolution of the disease.

Methods

Study design

Patients were recruited for this multi-center retrospective study from three hospitals designated for the treatment of COVID-19 namely Jinyintan Hospital in Wuhan, Shanghai Public Health Clinical Center in Shanghai and Tongling People's Hospital in Anhui Province, China. The recruitment period was from January 1 to February 15, 2020. All patients enrolled in this study were diagnosed as COVID-19 according to the diagnostic criteria from the fifth version of the guidelines on the Diagnosis and Treatment of COVID-19 by the National Health Commission of China. The study was approved by the Shanghai Public Health Clinical Center Ethics Committee, Jinyintan Hospital Ethics Committee, and the Tongling People's Hospital Ethics Committee, respectively.

COVID-19 clinical classification

According to the fifth version of the guidelines on the Diagnosis and Treatment of COVID-19 by the National Health Commission of, COVID-19 severity is classified as follows**:**

1. Mild type

The clinical symptoms are mild with no abnormal radiological findings.

2. Moderate type

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Fever, cough and other symptoms are presented with pneumonia on chest computed tomography.

3. Severe type

The disease is classified as severe if one of the following conditions is met:

(1) Respiratory distress, respiratory rate ≥ 30 per min;

(2) Oxygen saturation on room air at rest ≤ 93%;

(3) Partial pressure of oxygen in arterial blood / fraction of inspired oxygen ≤ 300 mmHg.

4. Critical type

One of the following conditions has to be met:

(1) Respiratory failure occurs and mechanical ventilation is required;

(2) Shock occurs;

(3) Patients with other organ dysfunction needing intensive care unit monitoring treatment.

Based on the clinical information collected until February 15, 2020, the final date of enrollment, we classified our COVID-19 patients into three groups in this study: moderate group, severe group, and critical group.

Data Collection

Medical records of COVID-19 patients were reviewed and epidemiological, demographic, clinical, laboratory examination, and outcome data were collected by the research team from Ruijin hospital. As of Feb 15, clinical data collection was completed. Additional information

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was collected from attending doctors and immediate family members of patients. Yun Feng and Min Zhou from Ruijin hospital cross-checked the data. The Chinese CDC and local CDC labs made a definite diagnosis of COVID-19 by throat-swab specimens from the upper respiratory tract. Real-time Reverse Transcription Polymerase Chain Reaction Assay was used to confirm the COVID-19 (8) and exclude other viral infection. All patients underwent chest CT scan. Bronchoalveolar lavage fluid, bronchial aspirates, and sputum were sent for bacterial and viral examinations. Two radiologists were invited to interpret all chest CT scans independently and were blinded to the clinical information of each patient. In case of discordance, the opinion of a third radiologist was sought to reach a final decision. Data on prognosis and treatment were updated on March 21, 2020.

Measurements and Outcomes

The primary outcomes were discharge or death. The data include clinical characteristics and symptoms on admission, comorbidity, laboratory findings, immunological findings, treatment and outcomes, and chest CT scan findings.

Statistical analysis

Continuous variables were expressed as median with interquartile range (IQR), and categorical variables were reported as frequency and percentages (%). According to the latest Chinese guidelines, patients were divided into three groups, namely moderate, severe and critical groups. The single factor analysis of variance (ANOVA) or Kruskal-Wallis H test were used as appropriate to compare the difference among the three groups. Categorical data were analyzed either by Pearson Chi-square test or by Fisher's Exact Test. Two-tailed tests were performed

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two-sided to determine significance at the 5% level. Bonferroni's correction was used for pairwise comparison. All data analyses were carried out using IBM SPSS Statistics (Version 25.0) and R software (Version 3.6.0).

Results

Clinical characteristics and symptoms on admission

As of Feb 15, 2020, data of the 476 COVID-19 patients admitted by then to the three selected hospitals had been collected to be included in our study. As shown in the Table 1, the median age of the patients was 53 years (IQR, 40-64). Patients from the critical and severe groups were older than those from the moderate group. The critical group had higher percentage of patients aged ≥75 years than the moderate group. Male patients accounted for 56.9% of all patients. 89.3% of patients had "Wuhan-related exposures". The median number of days from the onset of illness (the first date of presenting COVID-19 related symptoms, such as fever, cough, diarrhea, etc) to diagnosis was 4 days (IQR, 2-7). The median number of days from illness onset to admission was 6 days (IQR, 4-10). Patients from the moderate and severe groups had lower CURB-65 scores than those from the critical group, while 48.6% of critical patients had a CRUB-65 score of 0. Patients from the moderate group presented with lower MuLBSTA scores than both severe and critical groups. Among clinical symptoms including fever, cough, sputum production, dry cough, pharyngalgia, chest pain, shortness of breath, hemoptysis, muscle pain, digestive symptoms, neurological symptoms and others, fever was the most common symptom (85.9%), followed by dry cough (59.4%). The percentage of patients with fever or shortness of breath was significantly higher in the severe group than in the moderate

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group.

Related comorbidities

Various comorbidities including hypertension, cardiovascular disease, diabetes, malignancy, cerebrovascular disease, immunosuppression, chronic obstructive pulmonary disease, and chronic nephropathy were investigated in this study. 205 patients (43.1%) included in the study had comorbidities (Table 2). The percentage of comorbidities was significantly different among the three groups ($p<0.001$). Compared with the moderate group, the percentage of comorbidities was higher in the critical group (67.1% vs 37.8%, $p<0.05$). There were more patients with hypertension in the critical group than in the moderate group (35.7% vs 20.7%, $p<0.05$). We further compared the use of antihypertensive drugs in COVID-19 patients with hypertension. The moderate group had a higher percentage of patients receiving either angiotensin II receptor blocker (ARB) or angiotensin-converting enzyme inhibitors (ACEI/ARB） than severe and critical groups.

Laboratory testing

The normal range of laboratory parameters are shown in Supplementary Table E1. Further analysis on laboratory findings in Table 3 indicated that levels of C-reactive protein, alanine aminotransferase, aspartate aminotransferase, total bilirubin, lactate dehydrogenase, myohemoglobin, D-dimer were much higher in the severe group and the critical group as compared with the moderate group. The critical group had a significantly higher percentage of patients showing elevated troponin, and higher levels of serum creatine kinase-MB, procalcitonin and brain natriuretic peptide than the moderate group. Other indexes including

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lymphocyte count, serum albumin, serum calcium were significantly lower in the severe group and the critical group. Patients with moderate disease had higher estimated glomerular filtration rate than critical patients.

Immunological findings

Total T lymphocyte counts and T cell subset values were different in the three groups. Compared with the moderate group, CD3 counts were significantly lower in the severe group and the critical group. In the critical group, CD4 counts (174, IQR 122-285) were lower than that of the moderate group (449, IQR 312-659); CD8 counts in the critical (125, IQR 59-213) and severe groups (179, IQR 106-286) were also lower than that of the moderate group (266, IQR 165-414). The percentages of CD3 and CD4 cells followed the same trend. There was no difference in IgG and IgA levels among the three groups, while there was a decreased trend in the level of IgM among severe and critical patients (Table 4).

Treatment and outcomes

286 (60.1%) patients received antiviral therapy within first 4 days. Antivirals used included lopinavir and tonavir, arbidol, darunavir, corbicostat and chloroquine. Most patients (67.0%) received antibacterial therapy, including moxifloxacin, ceftriaxone and azithromycin. 8 (1.7%) patients received antifungal therapy. Compared with the moderate group, more patients received antiviral agents within first 4 days than severe group, and more patients received antibiotics and corticosteriods in the critical and severe groups (Table 5). It was found that in moderate and severe groups, patients who were given antibiotics or corticosteriods had longer length of hospital stay than patients who did not (Supplementary Table E2). In the critical group,

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giving early antiviral treatment within first 4 days and not giving corticosteriods throughout the hospitalization period were associated with good prognosis; however, none of these two therapies had any association with disease progression to death or mechanical ventilation (Supplementary Table E3). All patients with moderate disease were given only oxygen via nasal cannula or no oxygenation support at all. In the severe group, 24 (44.4%) patients received high-flow oxygen treatment. In the critical group, 4 (5.7%) patients received extracorporeal membrane oxygenation rescue therapy and 39 (55.7%) were given invasive mechanical ventilation. As of March 21, 2020, 403 (84.7%) patients had been discharged, 38 (8%) had died, 23 (4.8%) were still in hospital and 12 (2.5%) patients were lost to follow due to transfer to other facilities or losing contact. Critical patients had a higher percentage of bacterial co-infections and a higher mortality rate than patients with severe or moderate disease; they also had a longer hospital stay than patients from the moderate group. Patients were divided into four age groups for Kaplan-Meier survival curve analysis: <45 years, 45-64 years, 65-74 years and ≥75 years. The ≥75 years group had significantly lower survival rate than the other three groups (Supplementary Figure E1). In our multivariate cox regression model (Supplementary Table E4), age ≥75 years (hazard ratio, 6.07; 95% CI, 1.65-22.35; p=0.007), creatine kinase (1.01; 1.01-1.02; p=0.032), lactate dehydrogenase (1.002; 1-1.004; p=0.044) are associated with higher risk of in-hospital mortality.

CT findings on admission and dynamic changes

On admission, chest CT scan was performed to estimate the patients' condition and degree of lung involvement (Table 6). In the severe and critical groups, most patients had multiple lung lobes involved (5, IQR 5-5). More patients had pleural effusions in

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the critical groups compared to the moderate group (18% vs 3.1%, p<0.05). To monitor the changes of CT images during the whole process, we collected a patient's dynamic changes of CT images in the severe group from Shanghai Public Health Clinical Center from onset to improvement of the disease. As shown in Figure 1, the patient had ground-glass opacity on chest CT in the early stage of the disease. Consolidation was noted on chest CT during disease progression. Finally, the patient had linear opacity on day 29 from onset of illness.

Comparisons between patients from hospitals inside and outside Hubei

In our study, 300 patients were admitted in hospitals outside Hubei, and 176 patients were from a hospital in Hubei (Supplementary Table E5). The percentages of critical patients in hospitals outside and inside Hubei were 5% and 31.3%, respectively. Compared with patients in Wuhan hospital, patients in hospitals outside Hubei were younger and less likely to present with shortness of breath on admission, had shorter length of time from onset of illness to the time when diagnosis was confirmed or when they were admitted (Supplementary Figure E2). Patients outside Hubei also had less comorbidies. In terms of treatment, antibiotics and corticosteroids were prescribed less frequently to patients in hospitals outside Hubei (53% vs 90.9%, p<0.001; 19% vs 39.8%, p<0.001). Patients in hospitals outside Hubei had lower mortality rates in each severity group than those in Wuhan hospital (Supplementary Table E6). In hospitals outside Hubei, moderate patients had a shorter hospital stay while severe and critical patients had longer hospital stays.

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Stratified analysis by age

As shown in Supplementary Table E7, there was no difference in sex distribution among the four age groups. The ≥75 years group had a higher percentage of critical patients, with a higher percentage of comorbidities and death. The percentage of chronic obstructive pulmonary disease patients increased with age. There was a significant difference in smoking history among the four age groups (p=0.014). The distribution of alcohol consumption among four groups had no statistical difference. The levels of lymphocytes and IgM, as well as the percentage of patients presenting with $< 1\times10^9$/L lymphocyte count showed significant differences among the four age groups. In the <45 years group, patients had higher lymphocyte count and IgM levels, and less patients had decreased lymphocyte count. The ratio of bilateral lung involvement, the number of involved lung lobes, as well as the presence of consolidation, linear opacity and pleural effusion on CT scan among four age groups differed significantly.

Discussion

This study summarizes the clinical characteristics, laboratory tests, dynamic changes of CT images, treatment and prognosis of COVID-19 patients in two eastern China cities and in the city of disease onset, Wuhan. COVID-19 patients were divided into moderate group, severe group, and critical group according to the criteria set in the fifth edition of the guidelines on the Diagnosis and Treatment of COVID-19 issued by the National Health Commission of China.

Patients in the severe and critical groups had more comorbidities, especially diabetes and hypertension. ACEIs and ARBs were commonly used antihypertensive drugs. Angiotensin-

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converting enzyme 2 (ACE2) is a component of the renin-angiotensin system that is expressed in the heart and plays an important role in cardiac function. ACE2 is the host receptor of SARS-CoV-2 (9,10). It was reported that ACE2 is also the receptor of SARS and NL63 (11,12,13). COVID-19 has higher affinity than SARS-CoV (14) for ACE2. Recently Zhao *et al*. showed that ACE2 virus receptor expression is concentrated in a small population of type II alveolar cells by using single-cell RNA-Seq technique (15). It was reported that ACE inhibitor therapy could increase cardiac ACE2 mRNA expression, while losartan increased cardiac ACE2 activity (16). Compared with other antihypertensive drugs, whether ACEI/ARB would aggravate COVID-19 is not clear. In this study, the use of antihypertensives in COVID-19 patients was evaluated for the first time. The proportion of patients taking antihypertensives is higher in the moderate group. There are more patients taking ACEI/ARB in the moderate group. More case studies are needed in the future to further extend our preliminary conclusion . The mechanism and relationship between antihypertensives and the severity of COVID-19 remain to be studied.

In this study, we demonstrated that systemic organ indexes including levels of T lymphocytes, D-dimer, C-reactive protein, aspartate aminotransferase, myohemoglobin, $CD3^+$, $CD4^+$, $CD8^+$ were associated with COVID-19 severity. These laboratory findings demonstrated that patients with COVID-19 also had impaired cardiac, liver, haematological and cellular immune system function as previously reported (7). Previous studies showed that depletion of $CD8^+$ T cells protects and depletion of macrophages exacerbates MERS-CoV-induced pathology and clinical symptoms of disease (17). SARS-CoV-specific memory $CD8^+$ T cells protect susceptible hosts from lethal SARS-CoV infection (18). Dramatic loss of $CD4^+$ T (~90–100%

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of patients) and $CD8^+$ T cells (~80–90% patients) were found in comparison to the healthy control individuals during SARS infection (19,20,21). We also found that $CD3^+$, $CD4^+$, $CD8^+$ T cells were significantly reduced in severe and critical COVID-19 patients, but immunoglobulins were less affected as previously reported (22).

CT scan showed dynamic changes from the ground-glass opacification to consolidation, and then absorption of the lesions or change into the linear opacity. For the first time, CT images of COVID-19 were observed and recorded in real time. In this study, we found that more lung lobes were involved in the severe and critical groups compared with the moderate group, which was consistent with other research results (7). We also demonstrated that the percentage of patients with pleural effusion was significantly higher in the severe and critical groups than in the moderate group for the first time. Previous studies also showed that pleural effusion was a poor prognostic indicator in H5N1 infection (23).

Previous report showed that none of the scores to assess severity of illness such as pneumonia severity index or CURB-65 score has a good predictive ability in Influenza pneumonia (24,25). Our result showed that CURB-65 score was associated with the severity of COVID-19, but the difference in scores among three groups was small. The variance of MuLBSTA score (4,26), an early warning model for predicting mortality in viral pneumonia, among three groups is significant, and may therefore have a better predictive value.

Comparing patients in Hubei and those outside Hubei shows that early isolation, early diagnosis and early management might contribute to a decrease in the spread and progression of COVID-19. Our study also stratified COVID-19 patients based on the age. Patients over 75

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years old had more severe disease and had a higher risk of death. Age over 75 was also an important index contributing to the mortality risk. These results were consistent with previous studies (4,27,28).

Several limitations need to be addressed in further research. First, due to the limited number of cases, some of conclusions are preliminary, especially the influence of antihypertensive drugs ACEI/ARB on COVID-19. These results need to be further validated with more patients. Second, although prognosis and treatment on outcomes have been updated, the effect of antiviral agents and corticosteriods need further validation. Prospective studies should be performed to get more accurate results. Third, we only analyzed dynamic changes of CT images in a patient with marked improvement. More cases need to be analyzed to obtain more information.

In conclusion, this multi-center retrospective study demonstrated that severe and critical patients are older and have more comorbidities. Multiple organ dysfunction and immune dysfunction are the characteristics of severe and critical patients. The proportion of patients taking antihypertensives is higher in patients with moderate disease. There were more patients taking ACEI/ARB in the moderate group. The severe and critical patients had more lung lobes involved and pleural effusion. These clinical features are helpful for the diagnosis and treatment of COVID-19.

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Declaration of interests

None.

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Figure 1.

Cross-sectional unenhanced chest computed tomography images of a 30-year-old male patient with severe COVID-19 in different stages. (A) At early stage, bilateral, peripheral patchy ground-glass opacities (GGO) and consolidations were noticed on admission, and denser GGO (B) and predominant consolidation with inside air bronchogram sign occurred in two weeks after illness onset (C). The lesions were gradually absorbed later from day 19 (D) and day 25 (E). Linear opacities still remained within GGO which previously manifested as consolidation at the end of our observation (F).

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Table 1: Clinical Characteristics of 476 COVID-19 patients

Characteristics	All (n=476)	Disease Severity			P value
		Moderate (n=352)	Severe(n=54)	Critical (n=70)	
Median age (IQR) - yrs	53(40-64)	51(37-63)	58(48-67)	61(49-68)	＜0.0001
Age group - no. /total no.(%)					< 0.001
＜40 yrs	118/476(24.8)	107/352(30.4)*†	5/54(9.3)	6/70(8.6)	-
40-64 yrs	240/476(50.4)	172/352(48.9)	29/54(53.7)	39/70(55.7)	-
65-74 yrs	84/476(17.6)	56/352(15.9)	15/54(27.8)	13/70(18.6)	-
≥75 yrs	34/476(7.1)	17/352(4.8)*	5/54(9.3)	12/70(17.1)	-
Sex - no./total no.(%)					0.064
Male	271/476(56.9)	190/352(54)	33/54(61.1)	48/70(68.6)	-
Female	205/476(43.1)	162/352(46)	21/54(38.9)	22/70(31.4)	-
Wuhan-related exposure - no./total no.(%)‡	425/476(89.3)	312/352(88.6)	48/54(88.9)	65/70(92.9)	0.578
Days from illness onset to diagnosis confirmed - median days (IQR)	4(2-7)	4(2-7)	4(2-6)	2(0-7)	0.024
Days from illness onset to admission - median days (IQR)	6(4-10)	6(3-10)	7(4-10)	9(7-13)	0.0001
CURB-65 on admission - median days (IQR)	0(0-1)	0(0-0)*	0(0-1)*	1(0-1)	< 0.001
0	351/474(74.1)	280/350(80.0)	37/54(68.5)	34/70(48.6)	< 0.001
1-2	118/474(24.9)	70/350(20.0)	17/(31.5)	31/70(44.3)	-
3-4	5/474(1.0)	0	0	5/70(7.1)	-
MuLBSTA on admission - median days (IQR)	7(5-9)	7(5-9)*†	9(7-11)	11(7-13)	< 0.001
Habits					
Smoking - no./total no.(%)	44/454(9.7)	27/333(8.1)	7/53(13.2)	10/68(14.7)	0.161
Smoking years - yrs	20(10-30)	20(10-30)	30(20-40)	23(18-30)	0.119
Alcohol consumption - no./total no.(%)	37/454(8.1)	20/333(6)*	6/53(11.3)	11/68(16.2)	0.014
Symptoms - no./total no.(%)					
Fever	390/454(85.9)	277/337(82.2)*†	49/51(96.1)	64/66(97)	＜0.0001
Shivering	24/374(6.4)	17/300(5.7)	2/35(5.7)	5/39(12.8)	0.25
Sputum production	161/453(35.5)	100/336(29.8)*	20/50(40)	41/67(61.2)	＜0.0001
Dry cough	269/453(59.4)	220/336(65.5)*	28/50(56)	21/67(31.3)	＜0.0001
Pharyngodynia	35/433(8.1)	26/330(7.9)	3/45(6.7)	6/58(10.3)	0.83
Chest pain	21/440(4.8)	13/335(3.9)	5/47(10.6)	3/58(5.2)	0.13
Shortness of breath	109/447(24.4)	50/335(14.9)*†	14/48(29.2)*	45/64(70.3)	＜0.0001
Hemoptysis	5/435(1.1)	2/332(0.6)	1/45(2.2)	2/58(3.4)	0.089
Myalgia	55/438(12.6)	38/333(11.4)	4/46(8.7)	13/59(22)	0.054
Digestive symptoms	49/446(11)	39/336(11.6)	6/48(12.5)	4/62(6.5)	0.47
Neurological symptoms	47/440(10.7)	35/334(10.5)	6/46(13)	6/60(10)	0.84

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Table 1: P values denoted the comparison between moderate, severe and critical groups. * and † refer to P<0.05. There are post-hoc comparisons. *Comparison between the critical group and the moderate or severe group; †Comparison between the severe group and the moderate group. ‡Wuhan-related exposure: lived in Wuhan, had a travel history from Wuhan or had a person-to-person contact with people from Wuhan in the past 14 days.

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Table 2: Comorbidities of 476 COVID-19 patients

no./total no.(%)	All (n=476)	Disease Severity			P value
		Moderate (n=352)	Severe(n=54)	Critical (n=70)	
Any Comorbidity	205/476(43.1)	133/352(37.8)*	25/54(46.3)	47/70(67.1)	＜0.001
Hypertension	113/476(23.7)	73/352(20.7)*	15/54(27.8)	25/70(35.7)	0.02
ACEI	8/113(7.1)	7/8(87.5)	1/8(12.5)	0/8(0)	0.279
ARB	27/113(23.9)	23/27(85.2)	2/27(7.4)	2/27(7.4)	0.035
ACEI or ARB	33/113(29.2)	29/33(87.9)*	2/33(6.1)	2/33(6.1)	0.004
Other regimens	62/113(54.9)	35/62(56.5)	12/62(19.4)	15/62(24.3)	0.064
Cardiovascular disease	38/476(8)	21/352(6)*	5/54(9.3)	12/70(17.1)	0.007
Diabetes	49/476(10.3)	32/352(9.1)*	11/54(20.4)	6/70(8.6)	0.035
Malignancy	12/476(2.5)	5/352(1.4)*	1/54(1.9)	6/70(8.6)	0.002
Cerebrovascular disease	17/476(3.6)	8/352(2.3)*	1/54(1.9)	8/70(11.4)	0.001
Immunosuppression	7/476(1.5)	2/352(0.6)*	0/54(0)	5/70(7.1)	0.002
COPD	22/476(4.6)	8/352(2.3)*	3/54(5.6)	11/70(15.7)	< 0.001
Chronic nephropathy	4/476(0.8)	2/352(0.6)	1/54(1.9)	1/70(1.4)	0.279
Others	103/476(21.6)	63/352(17.9)*	17/54(31.5)	23/70(32.9)	0.004

Table 2: ACEI=angiotensin-converting enzyme inhibitors. ARB=angiotensin II receptor blocker. COPD=chronic obstractive pulmonary disease. P values denoted the comparison between moderate, severe and critical groups. * refers to P<0.05. There are post-hoc comparisons. Comparison between the critical group and the moderate group.

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Table 3: Laboratory findings of 476 COVID-19 patients

Median (IQR)	All (n=476)	Disease Severity			P value
		Moderate (n=352)	Severe(n=54)	Critical (n=70)	
C-reactive protein - mg/L	18.8(5.23-57)	12(4.17-37.37)*†	36.7(15.75-74.58)*	83.4(28.8-126.8)	< 0.0001
≥10 mg/L - no. /total no.(%)	266/415(64.1)	169/307(55)*†	38/45(84.4)	59/63(93.7)	< 0.0001
White blood cell count - $\times10^9$/L	5.29(4.22-7.02)	5.15(4.17-6.54)*	5.42(3.69-8.17)*	7.19(4.61-11.19)	< 0.0001
> 10×10^9/L - no. /total no.(%)	49/475(10.3)	23/351(6.6)*	7/54(13)	19/70(27.1)	< 0.0001
< 4×10^9/L- no. /total no.(%)	91/475(19.2)	67/351(19.1)	17/54(31.5)*	7/70(10)	-
Neutrophil count - $\times10^9$/L	3.56(2.61-5.42)	3.39(2.5-4.64)*	3.6(2.59-5.99)*	5.99(3.47-9.55)	< 0.0001
Lymphocyte count - $\times10^9$/L	1.03(0.7-1.45)	1.13(0.79-1.53)*†	0.78(0.52-1.08)	0.82(0.49-1.08)	< 0.0001
< 1.0×10^9/L- no. /total no.(%)	225/476(47.3)	136/352(38.6)*†	39/54(72.2)	50/70(71.4)	< 0.0001
Haemoglobin - g/L	132(121-144)	133(121-144)	132(123-144)	131(118-143)	0.704
Platelet count - $\times10^9$/L	184(145-238)	185(146-238)	184(138-216)	181(135-246)	0.666
ALT > 40μ/L	26(16-41)	23(15-38)*†	32(21-47)	35(25-53)	< 0.0001
AST > 40μ/L	28(21-39)	25(19-34)*†	34(26-53)	39(30-54)	< 0.0001
Total bilirubin - μmol/L	10.1(7.5-14)	9.5(7.3-13.3)*†	11.9(8.9-15.6)	12.2(8.6-16.7)	< 0.0001
Direct bilirubin - μmol/L	4(3.1-5.5)	3.9(3-5.5)	4.5(3.4-6.7)	4.1(3.1-5.5)	0.216
Albumin - g/L	37.87(32.8-41.84)	39.14(35.15-42.7)*†	35.93(32.05-39.56)*	32.25(27.88-34.35)	< 0.0001
urea - mmol/L	4.8(3.67-5.89)	4.6(3.6-5.59)*	4.8(3.96-5.84)	5.65(4.3-7.73)	< 0.0001
Creatinine - μmol/L	66.77(53.66-78.6)	65.46(52.96-76.66)	70.9(54.67-84.1)	67.95(55.23-81.28)	0.237
eGFR - ml/min/1.73m²‡	106(87-125)	108(92-128)*	102(89-118)	96(76-120)	0.001
Sodium - mmol/L	139(137-141)	139(137-141)	140(137-141)	140(137-142)	0.574
Potassium - mmol/L	3.9(3.6-4.2)	3.9(3.6-4.1)*	4(3.5-4.2)	4(3.7-4.6)	0.046
Calcium - mmol/L	2.04(1.96-2.15)	2.05(1.98-2.16)*†	2.03(1.89-2.07)	1.95(1.87-2.06)	< 0.0001
LDH - μ/L	259(202-356)	236(192-314)*†	307(228-401)*	378(275-523)	< 0.0001
Creatine Kinase - μ/L	82(55-148)	80(55-138)	98(57-154)	93(52-246)	0.468
CK-MB - μ/L	13(10.49-16.74)	12.75(10.07-15.95)*	14.11(11.31-19.25)	15.5(11.75-23)	0.001
Myohemoglobin - ng/ml	18.85(4.8-51.48)	11.7(3.65-40.2)*†	28.04(10.07-51.5)*	52.05(29.8-107.63)	< 0.0001
Troponin increased - no. /total no.(%)	86/384(22.4)	59/296(19.9)*	10/41(24.4)	17/47(36.2)	0.044
PCT - μg/L	0.05(0.02-0.08)	0.04(0.02-0.06)*	0.06(0.02-0.13)	0.07(0-0.18)	0.006
ESR - mm/h	48(30-80)	48(27-83)	45(33-79)	58(39-72)	0.7
BNP - pg/ml	40.85(21.64-79.37)	34.53(21.15-67.1)*	52.5(16.93-113.3)	49.9(34.45-120.4)	0.049
Lactic acid - mmol/L	2.75(2.23-3.27)	2.73(2.22-3.22)	3.09(2.37-3.62)	2.5(2.15-3.34)	0.308
Fibrinogen - g/L	4.4(3.65-5.41)	4.31(3.55-5.33)†	4.78(4.33-5.74)	4.71(3.89-5.74)	0.021
D-dimer - μg/L	0.58(0.35-1.48)	0.51(0.32-1.08)*†	0.89(0.44-2.33)	1.11(0.51-4)	< 0.0001

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Table 3: ALT=alanine transaminase. AST=aspartate aminotransferase. LDH=lactate dehydrogenase. PCT=procalcitonin. ESR=erythrocyte sedimentation rate. BNP=brain natriuretic peptide. P values denoted the comparison between moderate, severe and critical groups. * and † refer to P<0.05. There are post-hoc comparisons. *Comparison between the critical group and the moderate or severe group. †Comparison between the severe group and the moderate group. ‡eGFR calculated by abbreviated MDRD equation.

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Table 4: Immunological findings of 264 COVID-19 patients

Median (IQR)	All (n=253/476)‡	Disease Severity			P value
		Moderate (n=214/352)	Severe(n=26/54)	Critical (n=13/70)	
CD3⁺ cell counts - cell/μl	712(482-1036)	764(513-1069)*†	538(277-860)	323(186-512)	< 0.0001
CD4⁺ cell counts - cell/μl	418(273-636)	449(312-659)*	327(160-587)	174(122-285)	< 0.0001
CD8⁺ cell counts - cell/μl	247(155-388)	266(165-414)*†	179(106-286)	125(59-213)	< 0.0001
CD3⁺ cell percentage - %	68(60-75)	69(62-76)*	65(55-74)	56(40-64)	0.001
CD4⁺ cell percentage - %	40(33-47)	41(35-47)*	33(28-46)	29(23-39)	< 0.0001
CD8⁺ cell percentage - %	24(19-30)	25(19-30)	19(17-34)	22(13-29)	0.258
IgG - g/L	11.8(10.2-13.6)	11.8(10.3-13.6)	12.4(9.3-14.15)	10.9(9.97-13.1)	0.726
IgA - g/L	2.38(1.81-3.14)	2.46(1.82-3.1)	2.36(1.56-3.47)	2.24(1.91-2.99)	0.954
IgM - g/L	0.93(0.69-1.2)	0.94(0.7-1.21)	0.86(0.63-1.18)	0.68(0.55-0.99)	0.051

Table 4: CD=cluster of differentiation. Ig=Immunoglobulin. P values denoted the comparison between moderate, severe and critical groups. * and † refer to P<0.05. There are post-hoc comparisons. * Comparison between the critical group and the moderate or severe group. †Comparison between the severe group and the moderate group. ‡There are missing data.

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Table 5: Treatment and outcomes of 476 COVID-19 patients

	All (n=476)	Disease Severity			P value
		Moderate(n=352)	Severe(n=54)	Critical (n=70)	
Administration of antiviral - no./total no.(%)§	286/476(60.1)	199/352(56.5)†	40/54(74.1)	47/70(67.1)	0.021
Administration of antibiotics - no./total no.(%)	319/476(67)	209/352(59.4)*†	45/54(83.3)	65/70(92.9)	< 0.001
Administration of antifungus - no./total no.(%)	8/476(1.7)	2/352(0.6)*	0/54(0)	6/70(8.6)	< 0.001
Administration of corticosteroids - no./total no.(%)	127/476(26.7)	47/352(13.4)*†	28/54(51.9)*	52/70(74.3)	< 0.001
Oxygen therapy - no./total no.(%)					< 0.001
Nasal cannula or no oxygen therapy	368/476(77.3)	352/352(100)	15/54(27.8)	1/70(1.4)	-
High-flow nasal cannula	31/476(6.5)	0/352(0)	24/54(44.4)	7/70(10)	-
Non-invasive mechanical ventilation (ie, face mask)	34/476(7.1)	0/352(0)	15/54(27.8)	19/70(27.1)	-
Invasive mechanical ventilation	39/476(8.2)	0/352(0)	0/54(0)	39/70(55.7)	-
ECMO	4/476(0.8)	0/352(0)	0/54(0)	4/70(5.7)	-
Prognosis					< 0.001
Discharge from hospital	403/476(84.7%)	334/352(94.9%)*†	46/54(85.2%)*	23/70(32.9%)	-
Death	38/476(8%)	6/352(1.7%)*	3/54(5.6%)*	29/70(41.4%)	-
Remained in hospital	23/476(4.8%)	6/352(1.7%)†	4/54(7.4%)	13/70(18.6%)	-
Lost to follow-up	12/476(2.5%)	6/352(1.7%)*	1/54(1.9%)	5/70(7.1%)	-
Secondary bacterial infection‡	35/410(8.5%)	12/307(3.9%)*	4/48(8.3%)*	19/55(34.5%)	< 0.001
length of hospital stay – days	16(12-24)	15(12-22)*†	20(15-27)	21(12-48)	< 0.001

Table 5: ECMO=extracorporeal membrane oxygenation. P values denoted the comparison between moderate, severe and critical groups. * and † refer to P<0.05. There are post-hoc comparisons. * Comparison between the critical group and the moderate or severe group. †Comparison between the severe group and the moderate group. §Administration of antiviral refers to any antiviral drug usage in 4 days. ‡bacterial co-infection identified in BAL, bronchial aspirates and sputum.

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Table 6: Chest CT findings on admission of 476 COVID-19 patients

no./total no.(%)	All (n=476)	Disease Severity			p value
		Moderate (n=352)	Severe(n=54)	Critical (n=70)	
Bilateral lungs involved	373/442(84.4)	266/327(81.3)†	53/54(98.1)	54/61(88.5)	0.04
Lung lobes involved - median (IQR)	5(3-5)	5(3-5)	5(5-5)	5(5-5)	< 0.001
Consolidation	87/442(19.7)	68/327(20.8)	13/54(24.1)	6/61(9.8)	0.098
Ground-glass opacity	425/442(96.2)	311/327(95.1)	53/54(98.1)	61/61(100)	0.137
Linear opacity	129/442(29.2)	88/327(26.9)	19/54(35.2)	22/61(36.1)	0.206
Pleural effusion	25/442(5.7)	10/327(3.1)*	4/54(7.4)	11/61(18)	< 0.001
Pleural thickening	238/442(53.8)	176/327(53.8)	32/54(59.3)	30/61(49.2)	0.567

Table 6: P values denoted the comparison between moderate, severe and critical groups. * and † refer to P<0.05. There are post-hoc comparisons. *Comparison between the critical group and the moderate or severe group. †Comparison between the severe group and the moderate group.

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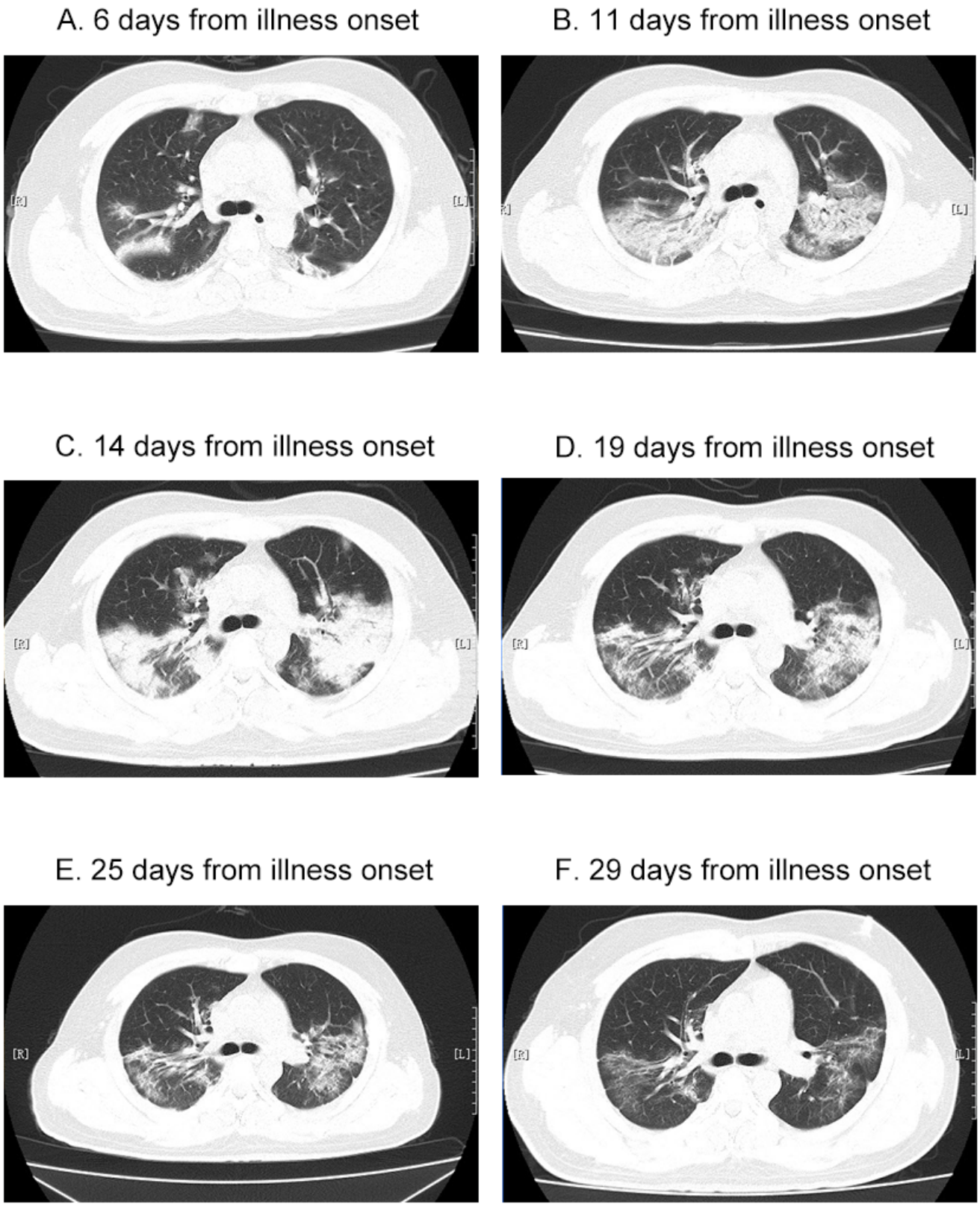

Figure 1

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COVID-19 with Different Severity: A Multi-center Study of Clinical Features

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Supplementary Table E1. Reference range of laboratory values

	Reference Range
C-reactive protein - mg/L	<3.00
White blood cell count - $\times 10^9$/L	3.50～9.50
Neutrophil count - $\times 10^9$/L	1.80～6.30
Lymphocyte count - $\times 10^9$/L	1.10～3.20
Haemoglobin - g/L	130.00～175.00
Platelet count - $\times 10^9$/L	125～350
ALT - μ/L	9.00～50.00
AST - μ/L	15.00～40.00
Total bilirubin - μmol/L	3.40～20.50
Direct bilirubin - μmol/L	0～8.60
Albumin - g/L	40.00～55.00
urea - mmol/L	3.60～9.50
Creatinine - μmol/L	57.00～111.00
eGFR - ml/min/1.73m²	> 90
Sodium - mmol/L	137.00 ~ 147.00

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Potassium - mmol/L	3.50 ~ 5.30
Calcium - mmol/L	2.10 ~ 2.55
LDH - μ/L	109.00 ~ 245.00
Creatine Kinase - μ/L	30.00 ~ 200.00
CK-MB - μ/L	0 ~ 24.00
Myohemoglobin - ng/ml	0 ~ 48.80
Troponin I - ng/ml	0 ~ 0.040
Troponin T - pg/ml	0 ~ 28
PCT - ug/L	0 ~ 0.05
ESR - mm/h	0 ~ 15
BNP - pg/ml	0 ~ 250.00
Lactic acid - mmol/L	0.50 ~ 2.20
Fibrinogen - g/L	2.00 ~ 4.00
D-dimer - μg/L	0 ~ 0.50
$CD3^+$ cell counts - cell/μl	690 ~ 2540
$CD4^+$ cell counts - cell/μl	410～1590
$CD8^+$ cell counts - cell/μl	190～1140

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$CD3^+$ cell percentage - %	53～84
$CD4^+$ cell percentage - %	31～60
$CD8^+$ cell percentage - %	13～41
IgG - g/L	7.00 ~ 16.00
IgA - g/L	0.70 ~ 4.00
IgM - g/L	0.40 ~ 2.30

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Supplementary Table E2. Treatments and outcomes in moderate and severe patients

	no./total no.(%)	Hospital length of stay - days	P value
Administration of antiviral			0.824
Provided	239/406(58.9)	16(12-23)	-
Not Provided	167/406(41.1)	16(12-23)	-
Administration of antibiotics			＜0.001
Provided	254/406(62.6)	17(13-24)	-
Not Provided	152/406(37.4)	15(11-20)	-
Administration of antifungus			NA
Provided	2/406(0.5)	5-8	-
Not Provided	404/406(99.5)	16(12-23)	-
Administration of corticosteroids			< 0.001
Provided	75/406(18.5)	22(17-32)	-
Not Provided	331/406(81.5)	15(11-22)	-

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Supplementary Table E3. Treatments and Outcomes in critical patients

	Discharge	Death	Remained in hospital	P value	Progression*	P value
Administration of antiviral				0.02		0.07
Provided	20/47(42.6)	18/47(38.3)	8/47(17)	-	43/47(91.5)	-
Not Provided	3/23(13)	11/23(47.8)	5/23(21.7)	-	17/23(73.9)	-
Administration of antibiotics				0.219		0.451
Provided	19/65(29.2)	28/65(43.1)	13/65(20)	-	55/65(84.6)	-
Not Provided	4/5(80)	1/5(20)	0/5(0)	-	5/5(100)	-
Administration of antifungus				0.449		1.00
Provided	3/6(50)	1/6(16.7)	2/6(33.3)	-	5/6(83.3)	-
Not Provided	20/64(31.3)	28/64(43.8)	11/64(17.2)	-	55/64(85.9)	-
Administration of corticosteroids				0.013		0.054
Provided	13/52(25)	21/52(40.4)	13/52(25)	-	42/52(80.8)	-
Not Provided	10/18(55.6)	8/18(44.4)	0/18(0)	-	18/18(100)	-

Supplementary Table E3: *Progression refers to mechanical ventilation or death.

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Supplementary Table E4. Cox Regression of factors associated with mortality

Characteristics and findings	HR(95%CI)	P value
Age (≥75 yrs vs. ＜75)	6.07(1.65-22.35)	0.007
Lymphocyte count (< 0.8×10^9/L vs. ≥0.8)	0.66(0.22-1.96)	0.455
D-dimer (＞1μg/L vs. ≤1)	3.26(0.99-10.72)	0.052
Creatine Kinase - μ/L	1.01(1.01-1.02)	0.032
LDH - μ/L	1.002(1-1.004)	0.044
Hypertension (Yes vs. No)	1.56(0.42-5.83)	0.511
Cardiovascular disease (Yes vs. No)	0.59(0.1-3.63)	0.568
Diabetes (Yes vs. No)	1.68(0.34-8.16)	0.522

Supplementary Table E4: 337 patients (16 deseased and 321 censored) with complete data of clinical interested variables were included in the bivariate Cox Proportional hazard ratio (HR) models for multivariate analysis of mortality. Laboratory findings on admission.

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Supplementary Table E5. Clinical features of 476 COVID-19 patients in different locations

	All (n=476)	Different Locations		p value
		Outside Hubei (n=300)	Hubei(n=176)	
Disease Severity				< 0.001
Moderate	352/476(73.9)	255/300(85)	97/176(55.1)	-
Severe	54/476(11.3)	30/300(10)	24/176(13.6)	-
Critical	70/476(14.7)	15/300(5)	55/176(31.3)	-
Clinical Characters				
Median age (IQR) - yrs	53(40-64)	50(36-64)	56(48-66)	< 0.001
Age group - no. /total no.(%)				< 0.001
< 40 yrs	118/476(24.8)	96/300(32)	22/176(12.5)	-
40-64 yrs	240/476(50.4)	138/300(46)	102/176(58)	-
65-74 yrs	84/476(17.6)	49/300(16.3)	35/176(19.9)	-
≥75 yrs	34/476(7.1)	17/300(5.7)	17/176(9.7)	-
Sex - no./total no.(%)				0.005
Male	271/476(56.9)	156/300(52)	115/176(65.3)	-

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Female	205/476(43.1)	144/300(48)	61/176(34.7)	-
Wuhan exposure history - no./total no.(%)	425/476(89.3)	249/476(83)	176/176(100)	NA
Days from illness onset to diagnosis confirmed - median days (IQR)	4(2-7)	4(2-7)	4(1-6)	0.031
Days from illness onset to admission - median days (IQR)	6(4-10)	4(2.5-7)	10(7-13.8)	< 0.001
Symptoms - no./total no.(%)				
Fever	390/454(85.9)	236/295(80)	154/159(96.9)	＜0.001
Shivering	24/374(6.4)	8/295(2.7)	16/79(20.3)	＜0.001
Sputum production	161/453(35.5)	75/291(25.8)	86/162(53.1)	< 0.001
Dry cough	269/453(59.4)	216/291(74.2)	53/162(32.7)	< 0.001
Pharyngodynia	35/433(8.1)	24/295(8.1)	11/138(8)	0.953
Chest pain	21/440(4.8)	10/295(3.4)	11/145(7.6)	0.052
Shortness of breath	109/447(24.4)	25/294(8.5)	84/153(54.9)	< 0.001
Hemoptysis	5/435(1.1)	1/295(0.3)	4/140(2.9)	0.039
Myalgia	55/438(12.6)	31/295(10.5)	24/143(16.8)	0.063
Digestive symptoms	49/446(11)	34/295(11.5)	15/151(9.9)	0.611
Neurological symptoms	47/440(10.7)	28/296(9.5)	19/144(13.2)	0.234

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Comorbidities				
Any Comorbidity	205/476(43.1)	117/300(39)	88/176(50)	0.019
Hypertension	113/476(23.7)	65/300(21.7)	48/176(27.3)	0.165
Cardiovascular disease	38/476(8)	31/300(10.3)	7/176(4)	0.014
Diabetes	49/476(10.3)	33/300(11)	16/176(9.1)	0.508
Malignancy	12/476(2.5)	3/300(1)	9/176(5.1)	0.006
Cerebrovascular disease	17/476(3.6)	5/300(1.7)	12/176(6.8)	0.003
Immunosuppression	7/476(1.5)	2/300(0.7)	5/176(2.8)	0.107
COPD	22/476(4.6)	12/300(4)	10/176(5.7)	0.399
Chronic nephropathy	4/476(0.8)	3/300(1)	1/176(0.6)	1
Others	103/476(21.6)	47/300(15.7)	56/176(31.8)	＜0.001
Treatments				
Administration of antiviral - no./total no.(%)	286/476(60.1)	181/300(60.3)	105/176(59.7)	0.885
Administration of antibiotics - no./total no.(%)	319/476(67)	159/300(53)	160/176(90.9)	＜0.001
Administration of antifungus - no./total no.(%)	8/476(1.7)	7/300(2.3)	1/176(0.6)	0.268
Administration of corticosteroids - no./total no.(%)	127/476(26.7)	57/300(19)	70/176(39.8)	＜0.001

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Oxygen therapy - no./total no.(%)				< 0.001
Nasal cannula or no oxygen therapy	368/476(77.3)	261/300(87)	107/176(60.8)	-
High-flow nasal cannula	31/476(6.5)	24/300(8)	7/176(4)	-
Non-invasive mechanical ventilation (ie, face mask)	34/476(7.1)	1/300(0.3)	33/176(18.8)	-
Invasive mechanical ventilation	39/476(8.2)	10/300(3.3)	29/176(16.5)	-
ECMO	4/476(0.8)	4/300(1.3)	0/176(0)	-
CT findings on addmission				
Bilateral lung involved- no./total no.(%)	373/442(84.4)	226/277(81.6)	147/165(89.1)	0.036
Lung lobes involved - median (IQR)	5(3-5)	4(2-5)	5(5-5)	< 0.001
Consolidation - no./total no.(%)	87/442(19.7)	83/277(30)	4/165(2.4)	< 0.001
Ground-glass opacity - no./total no.(%)	425/442(96.2)	262/277(94.6)	163/165(98.8)	0.026
Linear opacity- no./total no.(%)	129/442(29.2)	53/277(19.1)	76/165(46.1)	＜0.001
Pleural effusion - no./total no.(%)	25/442(5.7)	15/277(5.4)	10/165(6.1)	0.776
Pleural thickening- no./total no.(%)	238/442(53.8)	148/277(53.4)	90/165(54.5)	0.82

Supplementary Table E5: COPD=chronic obstractive pulmonary disease.ECMO=extracorporeal membrane oxygenation. P values denoted the comparison between Hubei and outside.

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Supplementary Table E6. Clinical Outcomes of 476 COVID-19 patients in different locations

				Disease Severity								
	All (n=476)			Moderate(n=352)			Severe(n=54)			Critical (n=70)		
no./total no.(%)	Outside Hubei(n=300)	Hubei(n=176)	P Value	Outside Hubei(n=255)	Hubei(n=97)	P Value	Outside Hubei(n=30)	Hubei(n=24)	P Value	Outside	Hubei(n=15)	Hubei(n=55)	P Value
Discharge from hospital	287/300(95.7%)	116/176(65.9%)	< 0.001	254/255(99.6%)	80/97(82.5%)	< 0.001	29/30(96.7%)	17/24(70.8%)	0.027	4/15(26.7%)	19/55(34.5%)	< 0.001	
Death	2/300(0.7%)	36/176(20.5%)	-	0/255(0%)	6/97(6.2%)	-	0/30(0%)	3/24(12.5%)	-	2/15(13.3%)	27/55(49.1%)	-	
Remained in hospital	11/300(3.7%)	12/176(6.8%)	-	1/255(0.4%)	5/97(5.2%)	-	1/30(3.3%)	3/24(12.5%)	-	9/15(60%)	4/55(7.3%)	-	
Lost to follow-up	0	12/176(6.8%)	-	0	6/97(6.2%)	-	0	1/24(4.2%)	-	0	5/55(9.1%)	-	
length of hospital stay – days	16(12-23)	18(13-27)	0.047	15(11-21)	18(14-27)	< 0.001	22(19-28)	15.5(10-23)	< 0.001	48(38-51)	18(11-30)	< 0.001	

Supplementary Table E6: P values denoted the comparison between Hubei and outside.

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Supplementary Table E7. Features of 476 COVID-19 patients in differernt Age groups

	Age - yrs				p value
	< 45 (n=118)	**45-64 (n=240)**	**65-74 (n=84)**	**≥75 (n=34)**	
Sex - no./total no.(%)					0.124
Male	78/118(66.1)	132/240(55)	43/84(51.2)	18/34(52.9)	-
Female	40/118(33.9)	108/240(45)	41/84(48.8)	16/34(47.1)	-
Disease Severity - no./total no.(%)					< 0.001
Moderate	107/118(90.7)	172/240(71.7)	56/84(66.7)	17/34(50)	-
Severe	5/118(4.2)	29/240(12.1)	15/84(17.9)	5/34(14.7)	-
Critical	6/118(5.1)	39/240(16.3)	13/84(15.5)	12/34(35.3)	-
Smoker - no./total no.(%)					0.014
Acute-smoker	4/114(3.5)	20/227(8.8)	7/79(8.9)	0/34(0)	-
Quit-smoker	0/114(0)	7/227(3.1)	3/79(3.8)	3/34(8.8)	-
Non-smoker	110/114(96.5)	200/227(88.1)	69/79(87.3)	31/34(91.2)	-
Alcohol consumption* - no./total no.(%)					0.147
Excessive-drinker	1/114(0.9)	4/227(1.8)	1/79(1.3)	1/34(2.9)	-

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Moderate-drinker	2/114(1.8)	19/227(8.4)	7/79(8.9)	2/34(5.9)	-
Non-drinker	111/114(97.4)	204/227(89.9)	71/79(89.9)	31/34(91.2)	-
Comorbidities - no./total no.(%)					
Any Comorbity	19/118(16.1)	97/240(40.4)	60/84(71.4)	29/34(85.3)	< 0.001
Hypertension	9/118(7.6)	50/240(20.8)	40/84(47.6)	14/34(41.2)	< 0.001
Cardiovascular disease	0/118(0)	12/240(5)	14/84(16.7)	12/34(35.3)	< 0.001
Diabetes	2/118(1.7)	19/240(7.9)	21/84(25)	7/34(20.6)	< 0.001
Malignancy	0/118(0)	4/240(1.7)	2/84(2.4)	6/34(17.6)	< 0.001
Cerebrovascular disease	1/118(0.8)	5/240(2.1)	4/84(4.8)	7/34(20.6)	< 0.001
Immunosuppression	1/118(0.8)	2/240(0.8)	3/84(3.6)	1/34(2.9)	0.175
COPD	0/118(0)	7/240(2.9)	9/84(10.7)	6/34(17.6)	< 0.001
Chronic nephropathy	0/118(0)	2/240(0.8)	1/84(1.2)	1/34(2.9)	0.276
Others	9/118(7.6)	52/240(21.7)	26/84(31)	16/34(47.1)	< 0.001
Hematology					
C-reactive protein - mg/L	7.37(3-19.05)	22.3(6.06-66.4)	38.7(14.65-73.65)	25(6.1-86.44)	< 0.001
≥10 mg/L - no. /total no.(%)	47/108(43.5)	142/207(68.6)	59/73(80.8)	18/27(66.7)	< 0.001

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White blood cell count - $\times 10^9$/L	5.17(4.22-6.78)	5.35(4.18-6.9)	5.32(4.09-7.51)	5.36(4.41-8.02)	0.937
＞10×10^9/L - no. /total no.(%)	21/118(17.8)	46/240(19.2)	19/83(22.9)	5/34(14.7)	0.793
＜4×10^9/L- no. /total no.(%)	11/118(9.3)	29/240(12.1)	6/83(7.2)	3/34(8.8)	-
Neutrophil count - $\times 10^9$/L	3.27(2.48-5)	3.59(2.64-5.47)	3.68(2.87-5.97)	3.96(2.78-6.18)	0.192
Lymphocyte count - $\times 10^9$/L	1.35(0.89-1.81)	0.99(0.72-1.37)	0.89(0.64-1.14)	0.82(0.56-1.45)	< 0.001
＜1.0×10^9/L- no. /total no.(%)	34/118(28.8)	121/240(50.4)	51/84(60.7)	19/34(55.9)	< 0.001
Immunology					
$CD3^+$ cell counts - cell/μl	1036(684-1418)	670(492-933)	553(307-788)	359(198-885)	< 0.001
$CD4^+$ cell counts - cell/μl	587(367-762)	410(291-600)	307(156-477)	195(116-613)	< 0.001
$CD8^+$ cell counts - cell/μl	407(255-563)	222(150-324)	194(129-261)	106(72-201)	< 0.001
$CD3^+$ cell percentage - %	71(65-78)	68(59-75)	64(54-72)	55(47-67)	< 0.001
$CD4^+$ cell percentage - %	40(34-45)	43(33-48)	38(31-45)	35(24-41)	0.034
$CD8^+$ cell percentage - %	28(25-31)	21(18-29)	22(16-32)	18(12-24)	< 0.001
IgG - g/L	11.9(10.2-13.9)	11.75(10.43-13.6)	11.1(9.97-12.4)	13(9.44-14.2)	0.383
IgA - g/L	2.26(1.77-3.04)	2.62(1.85-3.3)	2.31(1.64-3.23)	2.35(2.1-2.93)	0.336
IgM - g/L	1.04(0.8-1.35)	0.91(0.69-1.16)	0.82(0.49-1.08)	0.76(0.57-1.11)	0.003

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CT findings on admission - no./total no.(%)					
Bilateral lung involved	74/105(70.5)	194/226(85.8)	77/82(93.9)	28/29(96.6)	< 0.001
Lung lobes involved - medium (IQR)	4(2-5)	5(4-5)	5(5-5)	5(5-5)	< 0.001
Consolidation	30/105(28.6)	42/226(18.6)	12/82(14.6)	3/29(10.3)	0.039
Ground-glass opacity	101/105(96.2)	215/226(95.1)	80/82(97.6)	29/29(100)	0.723
Linear opacity	15/105(14.3)	76/226(33.6)	28/82(34.1)	10/29(34.5)	0.001
Pleural effusion	0/105(0)	12/226(5.3)	9/82(11)	4/29(13.8)	0.001
Pleural thickening	48/105(45.7)	127/226(56.2)	50/82(61)	13/29(44.8)	0.115
Prognosis - no./total no.(%)					< 0.001
Discharge from hospital	113/118(95.8)	203/240(84.6)	70/84(83.3)	17/34(50)	-
Death	3/118(2.5)	17/240(7.1)	8/84(9.5)	10/34(29.4)	-
Remained in hospital	0/118(0)	12/240(5)	4/84(4.8)	7/34(20.6)	-
Lost to follow-up	2/118(1.7)	8/240(3.3)	2/84(2.4)	0/34(0)	-

Supplementary Table E7: COPD=chronic obstractive pulmonary disease. CD=cluster of differentiation. Ig=Immunoglobulin.P values denoted the comparison between moderate, severe and critical groups. P values denoted the comparison between different age groups. *Definition by CDC on https://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm.

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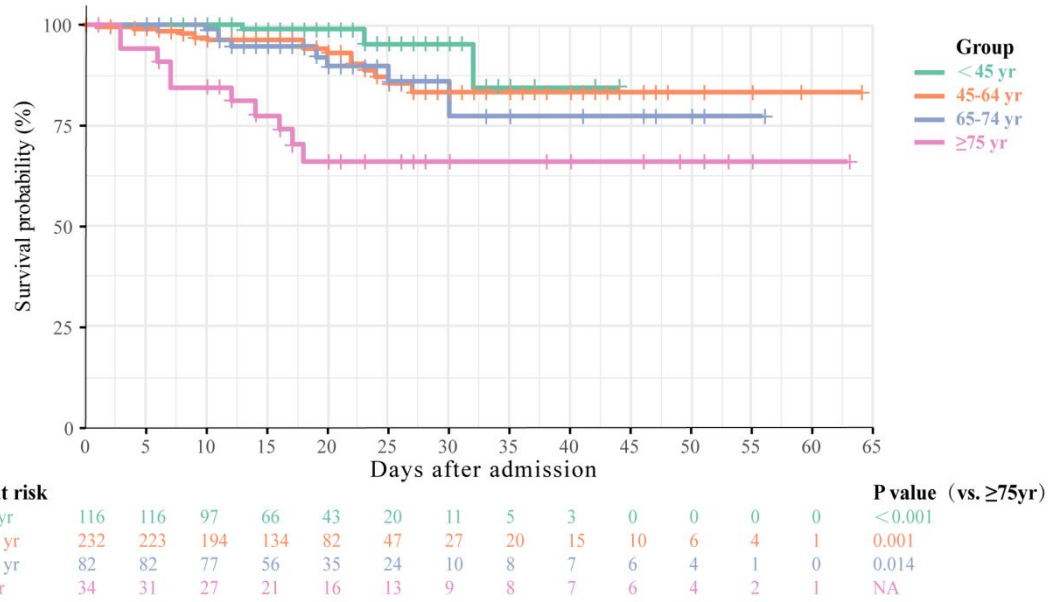
Supplementary Figure E1. Kaplan-Meier Survival Curve in COVID-19 patients among different age groups with log-rank test.



No. at risk														P value (vs. ≥75yr)
<45 yr	116	116	97	66	43	20	11	5	3	0	0	0	0	<0.001
45-64 yr	232	223	194	134	82	47	27	20	15	10	6	4	1	0.001
65-74 yr	82	82	77	56	35	24	10	8	7	6	4	1	0	0.014
≥75 yr	34	31	27	21	16	13	9	8	7	6	4	2	1	NA

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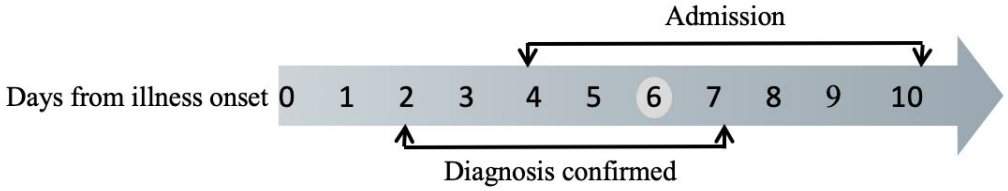
Supplementary Figure E2. Days from illness onset and admission in 476 COVID-19 patients



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