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ORIGINAL ARTICLE

COVID-19 with Different Severities: A Multicenter Study of Clinical Features

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Abstract

Rationale: The coronavirus disease (COVID-19) pandemic is now a global health concern.

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

Methods: A total of 476 patients were recruited from January 1, 2020, to February 15, 2020, at three hospitals in Wuhan, Shanghai, and Anhui. The patients were divided into four groups according to age and into three groups (moderate, severe, and critical) according to the fifth edition of the Guidelines on the Diagnosis and Treatment of COVID-19 issued by the National Health Commission of China.

Measurements and Main Results: The incidence of comorbidities was higher in the severe (46.3%) and critical (67.1%) groups than in the moderate group (37.8%). More patients were taking angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers in the moderate group than in the severe and critical groups. More patients had multiple lung lobe involvement and pleural effusion in the critical group than in the moderate group. More patients received antiviral agents within the first 4 days in the moderate group than in the severe group, and more patients received antibiotics and corticosteroids in the critical and severe groups. Patients >75 years old had a significantly lower survival rate than younger patients.

Conclusions: Multiple organ dysfunction and impaired immune function were the typical characteristics of patients with severe or critical illness. There was a significant difference in the use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers among patients with different severities of disease. Involvement of multiple lung lobes and pleural effusion were associated with the severity of COVID-19. Advanced age (⩾75 yr) was a risk factor for mortality.

Keywords: COVID-19; ACEI/ARB; severity; multiple lung lobe involvement; pleural effusion

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

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At a Glance Commentary

Scientific Knowledge on the Subject: Coronavirus disease (COVID-19) is posing an unprecedented threat to global healthcare systems. A number of observational studies have described clinical characteristics of patients with COVID-19 in single centers. However, details regarding the 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 ⩾75 years of age with COVID-19 had poor outcomes, and the in-hospital mortality rate among critical patients was 41.1%. Involvement of multiple pulmonary lobes and pleural effusion were associated with higher disease severity, whereas antihypertensive medication use was not. These clinical features should help clinicians identify high-risk patients.

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread throughout 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 receptor-binding domain structure similar to that of SARS-CoV, as shown by homology modeling (1). Zhou and colleagues found that 96% of SARS-CoV-2 is 96% identical at the whole-genome level to a bat coronavirus (2). COVID-19 was declared a public health emergency by the World Health Organization, and 4,006,257 laboratory-confirmed infections had been reported globally by May 12, 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 studies on COVID-19 cases were conducted in Wuhan, Hubei Province (1, 4, 5). Two recent studies summarized the findings regarding a large number of laboratory-confirmed SARS-CoV-2 infections in 31 provinces/provincial municipalities (6, 7). The Guidelines on the Diagnosis and Treatment of COVID-19 (fifth edition) 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 clinical features, laboratory examinations, computed tomography (CT) images, and use of therapies (including antiviral, antibacterial, and antifungal agents; corticosteroids; and antihypertensive medications) among three of the four groups (moderate type, severe type, and critical type) and four age groups of 476 patients with COVID-19 in three cities (Shanghai, Wuhan in Hubei Province, and Tongling in Anhui Province). We also summarize the dynamic changes observed in CT images of improved patients to characterize the evolution of the disease.

Methods

Study Design

Patients were recruited for this multicenter 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, 2020, to February 15, 2020. All patients enrolled in this study had received a diagnosis of COVID-19 according to the diagnostic criteria from the fifth edition 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, the Jinyintan Hospital Ethics Committee, and the Tongling People's Hospital Ethics Committee.

COVID-19 Clinical Classification

According to the fifth edition of the Guidelines on the Diagnosis and Treatment of COVID-19 by the National Health Commission of China, COVID-19 severity is classified as follows:

1. Mild type: The clinical symptoms are mild, with no abnormal radiological findings.
2. Moderate type: Fever, cough, and other symptoms are present with pneumonia on chest CT.
3. Severe type: The disease is classified as severe if one of the following conditions is met:
   - Respiratory distress, respiratory rate ⩾30/min.
   - Oxygen saturation on room air at rest ⩽93%.
   - Partial pressure of oxygen in arterial blood/F_{IO_2} ⩽300 mm Hg.
4. Critical type: One of the following conditions has to be met:
   - Respiratory failure occurs and mechanical ventilation is required.
   - Shock occurs.
   - Other organ dysfunction is present, requiring ICU monitoring and treatment.

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

Data Collection

Medical records of patients with COVID-19 were reviewed and epidemiological, demographic, clinical, laboratory examination, and outcome data were collected by the research team from Ruijin Hospital. As of February 15, collection of clinical data was completed. Additional information was collected from attending doctors and immediate family members of patients. Two of the authors (Y.F. and M.Z.) from Ruijin Hospital cross-checked the data. The Chinese Center for Disease Control and local Center for Disease Control labs made a definite diagnosis of COVID-19 by examining throat-swab specimens from the upper respiratory tract. Real-time RT-PCR assays were used to confirm COVID-19 (8) and exclude other viral infections. All patients underwent a chest CT scan. BAL 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 the case of discordance, the opinion of a third radiologist was sought to reach a final decision. Data regarding prognosis and treatment were updated on March 21, 2020.

Measurements and Outcomes

The primary outcomes were discharge or death. The data included clinical characteristics and symptoms on admission, comorbidities, laboratory findings, immunological findings, treatments 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 percentage. According to the latest Chinese guidelines, patients were divided into three groups: moderate, severe, and critical. Single-factor ANOVA or the Kruskal-Wallis H test were used as appropriate to assess differences among the three groups. Categorical data were analyzed either by Pearson's chi-squared test or by Fisher's exact test. Two-tailed tests were performed two-sided to determine significance at the 5% level. Bonferroni correction was used for pairwise comparisons. All data analyses were performed using IBM SPSS Statistics (version 25.0) and *R* software (version 3.6.0).

Results

Clinical Characteristics and Symptoms on Admission

As of February 15, 2020, data from the 476 patients with COVID-19 who had been admitted by then to the three selected hospitals had been collected to be included in this study. As shown in Table 1, the median age of the patients was 53 years (IQR, 40–64 yr). Patients in the critical and severe groups were older than those in the moderate group. The critical group had a higher percentage of patients aged ⩾75 years than the moderate group. Male patients accounted for 56.9% of all patients, and 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 d). The median number of days from illness onset to admission was 6 days (IQR, 4–10 d).

Table 1. Clinical Characteristics of 476 Patients with COVID-19

Characteristics	All (*N* = 476)	Disease Severity			*P* Value
		Moderate (*n* = 352)	Severe (*n* = 54)	Critical (*n* = 70)	
Median age, yr (IQR)	53 (40–64)	51 (37–63)	58 (48–67)	61 (49–68)	<0.0001
Age group, no./total no. (%)					<0.001
<40 yr	118/476 (24.8)	107/352 (30.4)*†	5/54 (9.3)	6/70 (8.6)	—
40–64 yr	240/476 (50.4)	172/352 (48.9)	29/54 (53.7)	39/70 (55.7)	—
65–74 yr	84/476 (17.6)	56/352 (15.9)	15/54 (27.8)	13/70 (18.6)	—
⩾75 yr	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 (IQR)	4 (2–7)	4 (2–7)	4 (2–6)	2 (0–7)	0.024
Days from illness onset to admission, median (IQR)	6 (4–10)	6 (3–10)	7 (4–10)	9 (7–13)	0.0001
CURB-65 on admission, median (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 (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	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

Definition of abbreviations: COVID-19 = coronavirus disease; CURB-65 = confusion, urea, respiratory rate, and blood pressure at age 65 years or older; IQR = interquartile range; MuLBSTA = multilobular infiltrates, lymphocyte, bacterial coinfection, smoking, hypertension, and age.

P values denote *post hoc* comparisons between the moderate, severe, and critical groups.

*$P < 0.05$, comparison between the critical group and the moderate or severe group.

†$P < 0.05$, comparison between the severe group and the moderate group.

‡Wuhan-related exposure: lived in Wuhan, had a history of travel from Wuhan, or had person-to-person contact with people from Wuhan in the past 14 days.

Patients from the moderate and severe groups had lower CURB-65 (confusion, urea, respiratory rate, and blood pressure at age 65 years or older) scores than those from the critical group, and 48.6% of critical patients had a CURB-65 score of 0. Patients from the moderate group presented with lower MuLBSTA (multilobular infiltrates, lymphocyte, bacterial coinfection, smoking, hypertension, and age) scores than both the 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, and neurological symptoms, fever was the most common (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 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. Among the patients included in the study, 205 (43.1%) had comorbidities (Table 2). The percentage of comorbidities was significantly different among the three groups ($P < 0.001$). The percentage of comorbidities was higher in the critical group than in the moderate 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%; $P < 0.05$). In addition, we assessed the use of antihypertensive drugs in patients with COVID-19 and hypertension. The moderate group had a higher percentage of patients receiving either angiotensin II receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACEI/ARB) than the severe and critical groups.

Laboratory Testing

The normal range of laboratory parameters are shown in Table E1 in the online supplement. Further analysis of the laboratory findings (Table 3) indicated that levels of C-reactive protein, alanine aminotransferase, aspartate aminotransferase, total bilirubin, lactate dehydrogenase, myohemoglobin, and D-dimer were much higher in the severe group and the critical group than in the moderate group. The critical group had a significantly higher percentage of patients showing elevated troponin, and higher levels of serum creatine kinase–myocardial band, procalcitonin, and brain natriuretic peptide than the moderate group. Other indexes, including lymphocyte count, serum albumin, and serum calcium, were significantly lower in the severe and critical groups. Patients with moderate disease had a higher estimated glomerular filtration rate than those with critical disease.

Immunological Findings

Total T-lymphocyte counts and T-cell subset values differed among the three groups. CD3 counts were significantly lower in the severe and critical groups than in the moderate group. CD4 counts (174; IQR, 122–285) were lower in the critical group than in the moderate group (449; IQR, 312–659). CD8 counts were lower in the critical (125; IQR, 59–213) and severe groups (179; IQR, 106–286) groups than in 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, but there was a trend toward decreased levels of IgM in the severe and critical groups (Table 4).

Treatment and Outcomes

A total of 286 patients (60.1%) received antiviral therapy within the first 4 days. The antivirals used included lopinavir and tonavir, arbidol, darunavir, corbicostat, and chloroquine. Most patients (67.0%) received antibacterial therapy, including moxifloxacin, ceftriaxone, and azithromycin. Eight patients (1.7%) received antifungal therapy. More patients received antiviral agents within the first 4 days in the moderate group than in the severe group, and more patients received antibiotics and corticosteroids in the critical and severe groups (Table 5). It was found that in the moderate and severe groups, patients who

Table 2. Comorbidities of 476 Patients with COVID-19

	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

Definition of abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease.

P values denote *post hoc* comparisons between the moderate, severe, and critical groups. Data are shown as no./total no. (%).

*$P < 0.05$, comparison between the critical group and the moderate group.

Table 3. Laboratory Findings of 476 Patients with COVID-19

	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, $\times 10^9$/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
$>10 \times 10^9$/L, no./total no. (%)	49/475 (10.3)	23/351 (6.6)*	7/54 (13)	19/70 (27.1)	<0.0001
$<4 \times 10^9$/L, no./total no. (%)	91/475 (19.2)	67/351 (19.1)	17/54 (31.5)*	7/70 (10)	—
Neutrophil count, $\times 10^9$/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, $\times 10^9$/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
$<1.0 \times 10^9$/L- no./total no. (%)	225/476 (47.3)	136/352 (38.6)*†	39/54 (72.2)	50/70 (71.4)	<0.0001
Hemoglobin, g/L	132 (121–144)	133 (121–144)	132 (123–144)	131 (118–143)	0.704
Platelet count, $\times 10^9$/L	184 (145–238)	185 (146–238)	184 (138–216)	181 (135–246)	0.666
ALT > 40 μ/L	26 (16–41)	23 (15–38)*†	32 (21–47)	35 (25–53)	<0.0001
AST > 40 μ/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/1.73 $m^{2‡}$	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

Definition of abbreviations: ALT = alanine transaminase; AST = aspartate aminotransferase; BNP = brain natriuretic peptide; CK-MB = creatine kinase–myocardial band; COVID-19 = coronavirus disease; eGFR = estimated glomerular filtration rate; ESR = erythrocyte sedimentation rate; IQR = interquartile range; LDH = lactate dehydrogenase; PCT = procalcitonin.

P values denote *post hoc* comparisons between the moderate, severe, and critical groups. Data are shown as median (IQR) unless otherwise noted.

*$P < 0.05$, comparison between the critical group and the moderate or severe group.

†$P < 0.05$, comparison between the severe group and the moderate group.

‡eGFR calculated by abbreviated Modification of Diet in Renal Disease equation. eGFR = 186 × (Creatinine/88.4)−1.154 × (age)−0.203 × (0.742 if female) × (1.210 if black).

received antibiotics or corticosteroids had longer hospital stays than those who did not (Table E2). In the critical group, giving early antiviral treatment within the first 4 days and not giving corticosteroids throughout the hospitalization period were associated with good prognosis; however, neither of these therapies had any association with disease progression to death or mechanical ventilation (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 patients (44.4%) received high-flow oxygen treatment. In the critical group, 4 patients (5.7%) received extracorporeal membrane oxygenation rescue therapy and 39 (55.7%) were given invasive mechanical ventilation. As of March 21, 2020, 403 patients (84.7%) had been discharged, 38 (8%) had died, 23 (4.8%) were still in the hospital, and 12 (2.5%) were lost to follow-up owing to transfer to other facilities or loss of contact. Critical patients had a higher percentage of bacterial coinfections and a higher mortality rate than patients with severe or moderate disease, and they also had longer hospital stays than patients from the moderate group. The 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 group of patients ⩾75 years of age had a significantly lower survival rate than the other three groups (Figure E1). In our multivariate cox regression model (Table E4), age ⩾75 years (hazard ratio, 6.07 [95% confidence interval (CI), 1.65–22.35]; $P = 0.007$), creatine kinase (hazard ratio, 1.01 [95% CI, 1.01–1.02]; $P = 0.032$), and lactate dehydrogenase (hazard ratio, 1.002 [95% CI, 1–1.004]; $P = 0.044$) were associated with a higher risk of in-hospital mortality.

CT Findings on Admission and Dynamic Changes

On admission, chest CT scans were performed to estimate the patients' condition and degree of lung involvement (Table 6). In the severe and critical groups, most patients showed involvement of multiple lung lobes (5 lung lobes; IQR, 5–5). More patients had pleural

Table 4. Immunological Findings from 264 Patients with COVID-19

	All (*n* = 253/476)*	Disease Severity			*P* Value
		Moderate (*n* = 214/352)	Severe (*n* = 26/54)	Critical (*n* = 13/70)	
$CD3^+$ cell counts, cells/μl	712 (482–1,036)	764 (513–1,069)†‡	538 (277–860)	323 (186–512)	<0.0001
$CD4^+$ cell counts, cells/μl	418 (273–636)	449 (312–659)†	327 (160–587)	174 (122–285)	<0.0001
$CD8^+$ cell counts, cells/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

Definition of abbreviations: CD = cluster of differentiation; COVID-19 = coronavirus disease; IQR = interquartile range.
P values denote *post hoc* comparisons between the moderate, severe, and critical groups. Data are shown as median (IQR).
*There are missing data.
†$P < 0.05$, comparison between the critical group and the moderate or severe group.
‡$P < 0.05$, comparison between the severe group and the moderate group.

effusions in the critical group than in the moderate group (18% vs. 3.1%; $P < 0.05$). To monitor the changes observed in CT images during the whole process, we examined the dynamic changes in CT images of a patient in the severe group from the Shanghai Public Health Clinical Center from onset to improvement of the disease. As shown in Figure 1, the patient had ground-glass opacities on chest CT in the early stage of the disease. Consolidation was noted on chest CT during disease progression. Finally, the patient had linear opacities on Day 29 from onset of illness.

Comparisons between Patients from Hospitals Inside and Outside of Hubei

In our study, 300 patients were admitted in hospitals outside of Hubei, and 176 patients were from a hospital in Hubei (Table E5). The percentages of critical patients in hospitals outside of and inside Hubei were 5% and 31.3%, respectively. Compared with patients in the Wuhan hospital, patients in hospitals outside of Hubei were younger and less likely to present with shortness of breath on admission and had shorter lengths of time from onset of illness to the time when the diagnosis was confirmed or they were admitted (Figure E2). Patients outside of Hubei also had fewer comorbidities. In terms of treatment, antibiotics and corticosteroids were prescribed less frequently to patients in hospitals outside of Hubei (53% vs. 90.9%; $P < 0.001$ and 19% vs. 39.8%; $P < 0.001$). Patients in hospitals

Table 5. Treatment and Outcomes of 476 Patients with COVID-19

	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 antifungal agent, 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)	—
Noninvasive mechanical ventilation (i.e., 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, no./total no. (%)					<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, no./total no. (%)§	35/410 (8.5)	12/307 (3.9)‡	4/48 (8.3)‡	19/55 (34.5)	<0.001
Length of hospital stay, d, median (IQR)	16 (12–24)	15 (12–22)†‡	20 (15–27)	21 (12–48)	<0.001

Definition of abbreviations: COVID-19 = coronavirus disease; ECMO = extracorporeal membrane oxygenation; IQR = interquartile range.
P values denote *post hoc* comparisons between the moderate, severe, and critical groups.
*"Administration of antiviral" refers to any antiviral drug use in the first 4 days.
†$P < 0.05$, comparison between the severe group and the moderate group.
‡$P < 0.05$, comparison between the critical group and the moderate or severe group.
§Bacterial coinfection identified in BAL, bronchial aspirates, and sputum.

Table 6. Chest Computed Tomography Findings on Admission of 476 Patients with COVID-19

	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

Definition of abbreviations: COVID-19 = coronavirus disease; IQR = interquartile range.
P values denote *post hoc* comparisons between the moderate, severe, and critical groups. Data are shown as no./total no. (%) unless otherwise noted.
*$P < 0.05$, comparison between the severe group and the moderate group.
†$P < 0.05$, comparison between the critical group and the moderate or severe group.

outside of Hubei had lower mortality rates in each severity group than those in the Wuhan hospital (Table E6). In hospitals outside of Hubei, patients with moderate disease had shorter hospital stays than those with severe or critical disease.

Stratified Analysis by Age

As shown in Table E7, there was no difference in sex distribution among the four age groups. The ⩾75 years group had a higher percentage of patients with critical disease, and a higher percentage of comorbidities and death. The percentage of patients with chronic obstructive pulmonary disease 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 the four groups had no statistical difference. The levels of lymphocytes and IgM, as well as the percentage of patients presenting with a lymphocyte count of $<1 \times 10^9$/L showed significant differences among the four age groups. In the <45 years group, patients had higher lymphocyte counts and IgM levels, and fewer patients had decreased lymphocyte counts. The ratio of bilateral lung involvement, the number of involved lung lobes, and the presence of consolidation, linear opacity, and pleural effusion on CT scans among the four age groups differed significantly.

Discussion

This study summarizes the clinical characteristics, laboratory tests, dynamic changes in CT images, treatments, and prognoses of patients with COVID-19 in two eastern China cities and in the city of disease onset, Wuhan. Patients with COVID-19 were divided into three groups (moderate, severe, and critical) 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.

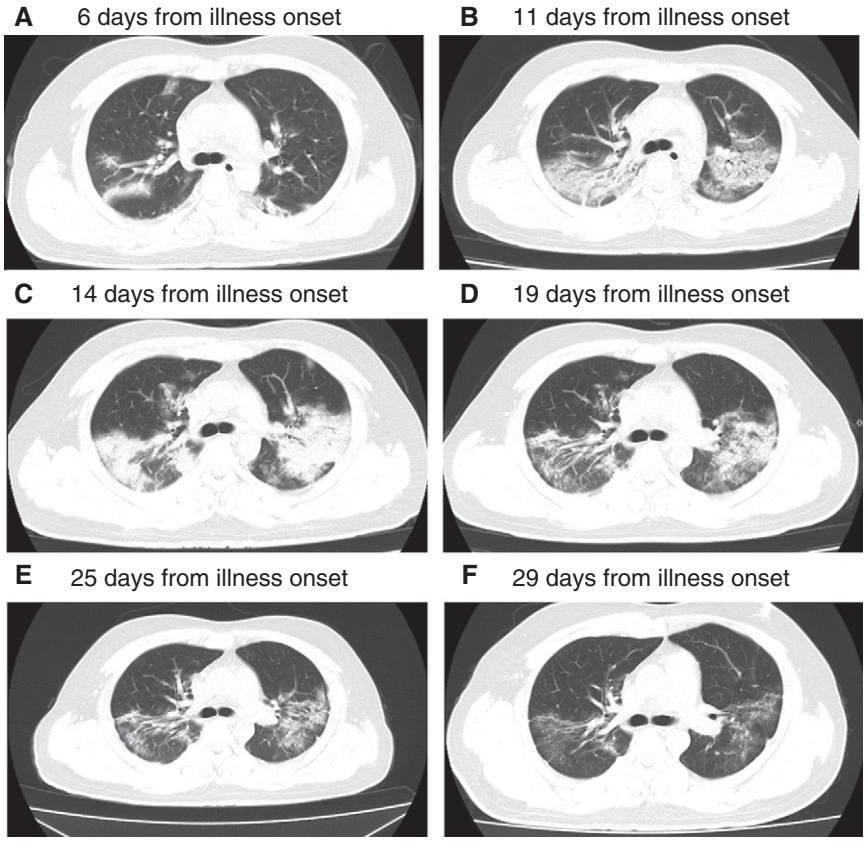

Figure 1. Cross-sectional, unenhanced chest computed tomography images of a 30-year-old male patient with severe coronavirus disease (COVID-19) in different stages. (*A–C*) In the early stage, bilateral, peripheral, patchy ground-glass opacities (GGO) and consolidations were noticed on admission (*A*), and denser GGO (*B*) and predominant consolidation with an inside air bronchogram sign (*C*) occurred within 2 weeks after illness onset. (*D* and *E*) The lesions were gradually absorbed later from Day 19 (*D*) to Day 25 (*E*). (*F*) Linear opacities still remained within GGO that previously manifested as consolidation at the end of our observation.

Patients in the severe and critical groups had more comorbidities, especially diabetes and hypertension. ACEIs and ARBs were commonly used antihypertensive drugs. ACE2 (angiotensin-converting enzyme 2) 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 (11–13). COVID-19 has a higher affinity than SARS-CoV (14) for ACE2. Recently, using a single-cell RNA-sequencing technique, Zhao and colleagues showed that ACE2 virus receptor expression was concentrated in a small population of type II alveolar cells (15). It was reported that ACE inhibitor therapy could increase cardiac ACE2 mRNA expression, and 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 patients with COVID-19 was evaluated for the first time. The proportion of patients taking antihypertensives was higher in the moderate group. There were 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, $CD3^+$, $CD4^+$, and $CD8^+$, were associated with COVID-19 severity. These laboratory findings demonstrated that patients with COVID-19 also had impaired cardiac, liver, hematological, and cellular immune system function, as previously reported (7). Previous studies showed that $CD8^+$ T cells protect against and depletion of macrophages exacerbates Middle East respiratory syndrome coronavirus–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 losses of $CD4^+$ T (~90–100% of patients) and $CD8^+$ T cells (~80–90% of patients) were found in patients with SARS infection compared with healthy control individuals (19–21). We also found that $CD3^+$, $CD4^+$, and $CD8^+$ T cells were significantly reduced in patients with severe or critical COVID-19, but immunoglobulins were less affected, as previously reported (22).

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

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

A comparison of patients inside and outside of Hubei showed 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 patients with COVID-19 based on age. Patients >75 years old had more severe disease and a higher risk of death. Age >75 years 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, given the limited number of cases, some of our conclusions are preliminary, especially regarding the influence of the antihypertensive drugs ACEI/ARB on COVID-19. These results need to be further validated with more patients. Second, although data regarding outcomes of prognosis and treatment have been updated, the effects of antiviral agents and corticosteroids require further validation. Prospective studies should be performed to obtain more accurate results. Third, we only analyzed dynamic changes in CT images of a patient with marked improvement. More cases need to be analyzed to obtain more information.

In conclusion, this multicenter, retrospective study demonstrated that patients with severe or critical disease were older and had more comorbidities. Multiple organ dysfunction and immune dysfunction were characteristic of patients with severe or critical disease. The proportion of patients who were taking antihypertensives was higher in the group with moderate disease, and more patients received ACEI/ARB in the moderate group. Patients with severe or critical disease 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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