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Time-dependent changes in the clinical characteristics and prognosis of hospitalized COVID-19 patients in Wuhan, China: A retrospective study

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ABSTRACT

Cases of coronavirus disease 2019 (COVID-19) have been breaking out around the world recently. However, the dynamic changes in the clinical symptoms and prognosis of COVID-19 patients remain unknown. According to the onset time of initial clinical symptoms, 843 COVID-19 patients admitted between Jan 22 and Feb 14, 2020 were divided into three groups: group A (Jan 21 to Jan 25, n = 324), group B (Jan 26 to Jan 31, n = 358) and group C (Feb 1 to Feb 10, n = 161). Data on the demographics, symptoms, first laboratory results, treatments and outcomes (within 12 days of hospitalization) were collected. The results showed that the median duration from symptom onset to admission shortened over time (13, 10 and 5 days, respectively, $p < 0.05$). Fewer patients had fever symptoms and bilateral pneumonia in group C than in the group A and B. Laboratory results showed that white blood cell, neutrophil, and platelet counts, lactic acid and D-dimer levels were lower, while lymphocyte, CD3, and CD8 counts were higher in group C. In addition, group C had more mild-moderate cases and fewer severe cases than the other two groups. More importantly, the incidence of complications (18.5%, 14.2% and 11.2%, respectively, $p < 0.05$) and all-cause mortality (11.7%, 8.4%, and 5.6%, respectively, $p < 0.05$) decreased over time. The clinical characteristics and prognosis of COVID-19 patients changed over time. Improved prognosis was found at a later stage.

1. Introduction

Last December 2019, several cases of viral pneumonia were found in Wuhan City, Hubei Province, which spread to most parts of China [1,2]. The gene sequence of the virus obtained from these patients shows that the new virus is a member of the coronaviruses and is classified in the beta-CoV lineage B, and it was subsequently renamed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Studies have shown that SARS-CoV-2 is similar to SARS-CoV and shares more than 79% of its sequence but only 50% homology with the coronavirus responsible for Middle East respiratory syndrome (MERS-CoV) [3,4]. On February 11, 2020, the World Health Organization (WHO) announced that pneumonia caused by SARS-CoV-2 was officially named coronavirus disease 2019 (COVID-19) [5].

Literature reports showed that the clinical characteristics of patients with COVID-19 included fever, nonproductive cough, dyspnea, fatigue, lymphopenia and radiographic evidence of pneumonia. Acute respiratory distress syndrome (ARDS), shock, acute cardiac injury, and acute kidney injury (AKI) were the main complications [6,7]. Z Zhang suggested that patients admitted after January 23 may have fewer systematic symptoms, such as fever, fatigue and myalgia [8]. In addition, a novel SARS-CoV-2 mutation (ORF3a) was found in Europe, indicating that the virus may evolve with time [9]. Therefore, the clinical characteristics of patients infected with SARS-CoV-2 may have subtly

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changed at later stages of the outbreak. In addition, comprehensive control measures were gradually implemented in Wuhan after January 23, which may be associated with a reduction in the epidemic and deaths [10]. Because of various factors, the outcomes of patients with COVID-19 may have been affected, which requires further study.

To figure out the dynamic change of clinical symptoms and outcomes of COVID-19 patients in Wuhan, we designed a retrospective study that recruited 843 patients with COVID-19 from the designated hospitals. According to the onset time of clinical symptoms, these patients were divided into three groups: group A (January 21 to January 25), group B (January 26 to January 31) and group C (February 1 to February 10). Then, we described the dynamic changes of clinical characteristics and compared the outcomes among the three groups, aiming to provide novel insights into the prevention and treatment of COVID-19.

2. Materials and methods

2.1. Data sources

We conducted a retrospective study focusing on the clinical characteristics, treatment and prognosis of consecutive confirmed patients with COVID-19 from Jan 22, 2020, to Feb 14, 2020 in Renmin Hospital of Wuhan University. Case definitions of confirmed COVID-2019 are in accordance with the "Diagnosis and treatment of novel coronavirus infected pneumonia (trial 6th edition)" formulated by the NHC of China [11]. Only patients with a laboratory-confirmed infection were enrolled in this study. The 843 patients were divided into three groups according to the onset time of initial symptoms: group A (January 21 to January 25), group B (January 26 to January 31) and group C (February 1 to February 10). January 25 and February 1 were chosen as a break point according to the important time points that could affect the spread of the SARS-CoV-2 [12], the numbers of symptomatic patients and the dynamic changes of different symptoms per day in our cohort. This study was approved by the Ethics Commission of Renmin Hospital of Wuhan University.

2.2. Target genes for real-time polymerase chain reaction assay for SARS-CoV-2

Two target genes, including open reading frame 1ab (ORF1ab) and nucleocapsid protein (N), were simultaneously amplified and tested during the real-time polymerase chain reaction (RT-PCR) assay. The RT-PCR assay was performed using the 2019-nCoV nucleic acid detection kits and the results were interpreted according to the manufacturers' protocols.

2.3. Data collection

Epidemiological, clinical, laboratory, and radiological characteristics and treatment and outcome data were obtained from medical records. The following information were collected: demographic data, medical history, underlying comorbidities, symptoms, signs, first laboratory findings, chest computed tomographic (CT) scans, and treatment measures (i.e., antiviral therapy, antibiotic therapy, corticosteroid and gamma globulin therapy, respiratory support, continuous renal replacement therapy). The clinical outcomes (i.e., discharge, mortality, still in hospital) were monitored within 12 days of hospitalization.

2.4. Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQRs). For categorical variables, we calculated the frequency rates and percentages of patients in each category. Continuous variables were compared using the Kruskal-Wallis test. Proportions for categorical variables were compared using the $\chi 2$ test and Fisher's exact test was used when the data were limited. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS 21.0.

3. Results

3.1. Presenting characteristics

There were 324 patients in group A, 358 patients in group B, and 161 patients in group C. The number of patients per day according to the initial date of symptoms was shown in Supplemental Fig. S1 and the dynamic changes of different symptoms was shown in Supplemental Fig. S2. The median age was 60 (48, 69) in group A, 61 (47, 70) in group B and 59 (39, 70) in group C, although group C had more patients aged less than 45 years. The results showed that the intervals from the onset of symptoms to admission exhibited a decreasing trend among the three groups (13 [10,15] vs. 10 [7,11] vs. 5 [4,8], $p < 0.05$). In addition, group C had fewer patients with fever (80.6% vs. 79.9% vs. 70.2%, $p < 0.05$) and fewer patients with respiratory rates >30 bpm (13.6% vs. 14.8% vs. 11.2%, $p < 0.05$) during hospitalization. However, other initial symptoms and signs on admission did not show significant differences among the three groups. Regarding comorbidity, the rate of patients with cerebrovascular diseases showed a decreasing trend (3.4% vs. 1.4% vs. 0.6%), and fewer patients with more than one comorbidity were found in group C. The clinical data for all patients is listed in Tables 1 and 2.

3.2. Results of laboratory tests and CT parameters

The first results of laboratory tests and CT parameters were analyzed. The blood rountine test results showed that the white blood cell count (median, 5.6 vs. 5.37 vs. 4.87 $\times 10^9$/L, $p < 0.05$), neutrophil count (median, 4.07 vs. 3.43 vs. 3.13 $\times 10^9$/L, $p < 0.05$) and platelet count (median, 215 vs. 207 vs. 193 $\times 10^9$/L, $p < 0.05$) were lower, and lymphocyte count (median, 0.98 vs. 0.98 vs. 1.08 $\times 10^9$/L, $p < 0.05$) was higher in group C than in group A and B. In addition, more than half of the patients had lymphopenia in all three groups. Group C had fewer patients with lymphopenia than the others, although the differences were not significant. In addition, lower alanine aminotransferase, aspartate aminotransferase, lactic acid, lactate dehydrogenase (LDH) and D-dimer levels and higher albumin, uric acid and Cl^- levels were observed in group C. Regarding immunoreactions, the results revealed that CD3 counts (median, 586 vs. 581 vs. 665 /μL, $p < 0.05$) and CD8 counts (median, 215 vs. 194 vs. 229 /μL, $p < 0.05$) were higher in group C. However, no significant differences were shown in the major items of humoral immunity and general markers of the inflammatory response (IL-6, IL-10, etc.). Fewer patients showed bilateral lesions (89.3% vs. 85.3% vs. 72.5%, $p < 0.05$) in the CT images in group C than in group A and group B, while there was no significant difference in air bronchus sign and consolidation lesions among the three groups. The laboratory tests and CT parameters for all patients are listed in Table 3–5.

3.3. Complications and treatment

In terms of treatment, compared with group A and B, fewer patients received mask oxygen inhalation (30.2% vs. 33.5% vs. 24.2%, $p < 0.05$) in group C. More patients received antiviral treatment (90.7% vs. 96.6% vs. 97.5%, $p < 0.05$) in both group B and C than in group A, although no significant differences were reported in other medical treatments. In addition, there was no difference in the use of nasal catheter oxygen inhalation, mechanical ventilation, continuous renal replacement therapy, extracorporeal membrane oxygenation and artificial liver support system among the three groups.

In addition, the incidence of complications was significantly lower in group C than in group A ($p < 0.05$). The proportion of patients with

Table 1
Baseline characteristics of COVID-19 patients.

	All (n = 843)	Group A (n = 324)	Group B (n = 358)	Group C (n = 161)
Male (n, %)	400 (47.4%)	163 (50.3%)	159 (44.4%)	78 (48.4%)
Age, median (IQR), y	60 (47, 70)	60 (48, 69)	61 (47, 70)	59 (39, 70)
Age group, No. (%)				
15–44 years	189 (22.4%)	67 (20.7%)	73 (20.4%)	49 (30.4%)#
45–64 years	316 (37.5%)	138 (42.6%)	134 (37.4%)	44 (27.3%)*
65–84 years	317 (37.6%)	114 (35.2%)	141 (39.4%)	62 (38.5%)
≥85 years	21 (2.5%)	5 (1.5%)	10 (2.8%)	6 (3.7%)
Onset of symptom to admission, median (IQR), d[a]	10 (7, 13)	13 (10, 15)	10 (7, 11) *	5 (4, 8) *#
Initial symptoms, No. (%)				
Fever	660 (78.3%)	261 (80.6%)	286 (79.9%)	113 (70.2%) *#
Symptoms of respiratory system				
Sore throat	33 (3.9%)	13 (4.0%)	14 (3.9%)	6 (3.7%)
Cough	513 (60.9%)	194 (59.9%)	229 (64.0%)	90 (55.9%)
Expectoration	160 (19.0%)	56 (17.3%)	76 (21.2%)	28 (17.4%)
Chest tightness	188 (22.3%)	65 (20.1%)	84 (23.5%)	39 (24.2%)
Chest pain	15 (1.8%)	5 (1.5%)	5 (1.4%)	5 (3.1%)
Dyspnea	218 (25.9%)	90 (27.8%)	89 (24.9%)	39 (24.2%)
Catarrhal symptoms	14 (1.7%)	8 (2.5%)	4 (1.1%)	2 (1.2%)
Neuromuscular symptoms				
Weakness	281 (33.3%)	102 (31.5%)	124 (34.6%)	55 (34.2%)
Dizziness	23 (2.7%)	5 (1.5%)	13 (3.6%)	5 (3.1%)
Headache	25 (3.0%)	9 (2.8%)	10 (2.8%)	6 (3.7%)
Muscle ache	50 (5.9%)	21 (6.5%)	24 (6.7%)	5 (3.1%)
Digestive symptoms				
Anorexia	100 (11.9%)	37 (11.4%)	44 (12.3%)	19 (11.8%)
Nausea	14 (1.7%)	5 (1.5%)	6 (1.7%)	3 (1.9%)
Vomiting	19 (2.3%)	9 (2.8%)	8 (2.2%)	2 (1.2%)
Abdominal pain	2 (0.2%)	0 (0.0%)	1 (0.3%)	1 (0.6%)
Diarrhea	92 (10.9%)	33 (10.2%)	42 (11.7%)	17 (10.6%)

The total number of patients with available data: *a*: n(A) = 324, n(B) = 358, n(C) = 161. *p < 0.05 vs. group A. #p < 0.05 vs. group B.

Table 2
Vital signs and comorbidity of COVID-19 patients.

	All (n = 843)	Group A (n = 324)	Group B (n = 358)	Group C (n = 161)
Characteristics on admission				
Fever, No. (%) [a]	168 (20.8%)	67 (20.7%)	68 (19.0%)	33 (20.5%)
Temperature, No. (%) [a]	36.7 (36.4, 37)	36.7 (36.4, 37)	36.7 (36.4, 37)	36.6 (36.4, 37.1)
<37.3 ℃	641 (79.2%)	233 (77.7%)	283 (80.6%)	125 (79.1%)
37.3–38.0 ℃	62 (7.7%)	25 (8.3%)	22 (6.3%)	15 (9.5%)
38.1–39.0 ℃	98 (12.1%)	38 (12.7%)	44 (12.5%)	16 (10.1%)
≥39.1 ℃	8 (1.0%)	4 (1.3%)	2 (0.6%)	2 (1.3%)
Heart rate, median (IQR), bpm[b]	82 (76, 91)	82 (76, 92)	82 (76, 90)	82 (76, 92)
Systolic pressure, median (IQR), mmHg[c]	126 (116, 139)	127 (117, 140)	126 (114, 138)	127 (116, 140)
Diastolic pressure, median (IQR), mmHg[d]	76 (68, 83)	76 (69, 84)	75 (68, 83)	74 (67, 80) *
Respiratory rate, median (IQR), bpm[e]	20 (18, 20)	20 (18, 20)	20 (18, 20)	19 (18, 20)
Finger oxygen saturation, median (IQR), %[f]	97 (95, 99)	97 (95, 99)	97 (95, 98)	98 (96, 99)
Characteristics during hospital admission, No. (%)				
Fever[g]	526 (65.1%)	207 (63.9%)	151 (60.3%)	103 (64.0%)
Highest temperature[g]				
<37.3 ℃	282 (34.9%)	92 (30.8%)	135 (38.5%)*	55 (34.8%)
37.3–38.0 ℃	308 (38.1%)	121 (40.5%)	132 (37.6%)	55 (34.8%)
38.1–39.0 ℃	164 (20.3%)	62 (20.7%)	65 (18.5%)	37 (23.4%)
≥39.1 ℃	54 (6.7%)	24 (8.0%)	19 (5.4%)	11 (7.0%)
Respiratory rate ≥ 30 bpm	115 (14.3%)	49 (13.6%)	48 (14.8%)	18 (11.2%)#
Comorbidity, No. (%)				
Diabetes	98 (11.6%)	38 (11.7%)	41 (11.5%)	19 (11.8%)
Hypertension	231 (27.4%)	94 (19.0%)	105 (29.3%)	32 (19.9%)*#
Coronary heart disease	48 (5.7%)	21 (6.5%)	22 (6.1%)	5 (3.1%)
COPD/asthma	24 (2.8%)	9 (2.8%)	9 (2.5%)	6 (3.7%)
Cerebrovascular disease	17 (2.0%)	11 (3.4%)	5 (1.4%)	1 (0.6%)#
Chronic renal disease	15 (1.8%)	3 (0.9%)	11 (3.1%)*	1 (0.6%)
Chronic liver disease	22 (2.6%)	7 (2.2%)	9 (2.5%)	6 (3.7%)
Malignancy	16 (1.9%)	6 (1.9%)	8 (2.2%)	2 (1.2%)
Autoimmune disease	9 (1.1%)	4 (1.2%)	4 (1.1%)	1 (0.6%)
Organ transplantation	2 (0.2%)	1 (0.3%)	1 (0.3%)	0 (0.0%)
Only one comorbidity	205 (24.3%)	67 (20.7%)	96 (26.8%)	42 (26.1%)
≥2 comorbidities	124 (14.7%)	55 (17.0%)	54 (15.1%)	15 (9.3%)*

The total number of patients with available data: *a*: n(A) = 300, n(B) = 351, n(C) = 158, *b*: n(A) = 300, n(B) = 350, n(C) = 158; *c*: n(A) = 266, n(B) = 296, n(C) = 132; *d*: n(A) = 267, n(B) = 298, n(C) = 132; *e*: n(A) = 299, n(B) = 350, n(C) = 158; *f*: n(A) = 252, n(B) = 290, n(C) = 121; *g*: n(A) = 299, n(B) = 351, n(C) = 158. *p < 0.05 vs. group A. #p < 0.05 vs. group B.

Table 3
General laboratory findings of COVID-19 patients on admission.

	Median (IQR)			
	ALL (n = 843)	Group A (n = 324)	Group B (n = 358)	Group C (n = 161)
Blood routine[a]				
White blood cell count, × 10^9/L	5.41 (4.09, 7.17)	5.60 (4.38, 7.59)	5.37 (4.06, 7.19)	4.87 (3.66, 6.35)*#
Neutrophil count, × 10^9/L	3.66 (2.43, 5.38)	4.07 (2.59, 6.13)	3.43 (2.48, 5.44)*	3.13 (2.14, 4.36)*#
Lymphocyte count, × 10^9/L	1.00 (0.71, 1.44)	0.98 (0.68, 1.40)	0.98 (0.68, 1.40)	1.08 (0.79, 1.53)*#
Platelet count, × 10^9/L	209 (164, 272)	215 (167, 281)	207 (163, 265)	193 (151, 255)*
Red blood cell count, × 10^{10}/L	4.10 (3.74, 4.45)	4.06 (3.76, 4.41)	4.10 (3.74, 4.49)	4.16 (3.71, 4.46)
Liver function[b]				
Alanine aminotransferase, U/L	25 (17, 43)	27 (18, 48)	24 (16, 40)*	21 (14, 36)*
Aspartate aminotransferase, U/L	28 (21, 41)	30 (21, 44)	28 (21, 41)	26 (20, 37)*
Total bilirubin, μmol/L[c]	10.4 (8.0, 14.2)	10.7 (8.1, 14.8)	10.1 (7.6, 14.0)	10.0 (8.0, 13.0)
Direct bilirubin, μmol/L	3.8 (2.7, 5.1)	3.9 (2.8, 5.4)	3.7 (2.6, 5.1)	3.8 (2.8, 4.9)
Albumin, g/L	36.9 (33.5, 39.8)	36.7 (33.6, 39.6)	36.6 (33.0, 39.7)	37.5 (34.5, 40.3)*#
Kidney function[d]				
Creatinine, μmol/L	61 (50, 73)	59 (49, 73)	61 (50, 72)	62 (51, 74)
Blood urea nitrogen, nmol/L	4.6 (3.6, 6.2)	4.7 (3.6, 6.0)	4.6 (3.7, 6.3)	4.4 (3.4, 6.1)
Uric acid, μmol/L	247 (199, 328)	235 (196, 319)	249 (195, 323)	257 (215, 347)*
Estimated glomerular filtration rate, mL/min	98.7 (88.5, 111.4)	100.1 (90.2, 111.6)	97.1 (87.0, 108.3)	98.9 (88.3, 113.9)
Injury of cardiac and skeletal muscle				
Creatine kinase, U/L[e]	62 (39, 107)	60 (37, 103)	61 (40, 105)	64 (43, 118)
Creatine kinase-myocardial isoenzyme mb, ng/mL[f]	1 (0.6, 1.8)	0.91 (0.62, 1.56)	1.03 (0.65, 1.9)	1 (0.65, 1.83)
Lactate dehydrogenase, U/L[g]	270 (211, 371)	276 (214, 386)	270 (210, 376)	251 (202, 347)*
Myoglobin, μg/L [h]	44.1 (28.8, 85.1)	42.4 (28.1, 73.0)	45.6 (29.4, 89.8)	46.0 (27.5, 79.9)
Hypersensitive troponin I,ng/mL [i]	0.006 (0.006, 0.017)	0.006 (0.006, 0.018)	0.006 (0.006, 0.016)	0.006 (0.006, 0.017)
Arterial Blood Gas Analysis[j]				
Blood PH	7.42 (7.38, 7.45)	7.42 (7.37, 7.46)	7.42 (7.38, 7.45)	7.42 (7.38, 7.45)
Arterial oxygen saturation, %	96 (91, 98)	95 (90, 98)	96 (92, 98)	97 (92, 98)
Lactic acid, mmol/L [k]	2.2 (1.6, 2.9)	2.4 (1.8, 3.4)	2.2 (1.6, 2.8)*	1.9 (1.4, 2.4)*#
Electrolytes[l]				
K+, mmol/L	3.8 (3.4, 4.2)	3.9 (3.4, 4.3)	3.8 (3.4, 4.3)	3.8 (3.4, 4.1)
Na+, mmol/L	139 (136, 142)	140 (137, 142)	139 (136, 142)	140 (136, 142)
Cl -, mmol/L [m]	105.5 (102.7, 107.8)	105.3 (102.7, 107.8)	105.2 (102.5, 107.5)	106.5 (103.8, 108.4)*#
Coagulation function[n]				
Prothrombin time activity, % [o]	83.2 (74.9, 91.6)	82.1 (73.8, 91.4)	84.0 (76.0, 93.2)	84.4 (74.1, 92.7)
Activated partial thromboplastin time, s	28.5 (26.3, 31.3)	27.9 (25.7, 31)	28.5 (26.3, 31.5)	29.3 (27.3, 32.2)*#
D-dimer, μmol/L	0.79 (0.41, 2.19)	0.91 (0.47, 3.55)	0.78 (0.39, 1.89)*	0.60 (0.34, 1.30)*

The total number of patients with available data: *a*: n(A) = 321, n(B) = 349, n(C) = 157, *b*: n(A) = 321, n(B) = 347, n(C) = 160; *c*: n(A) = 320, n(B) = 347, n(C) = 159; *d*: n(A) = 320, n(B) = 347, n(C) = 160; *e*: n(A) = 316, n(B) = 340, n(C) = 158; *f*: n(A) = 254, n(B) = 287, n(C) = 120; *g*: n(A) = 315, n(B) = 341, n(C) = 158; h: n(A) = 253, n(B) = 285, n(C) = 119; i: n(A) = 254, n(B) = 287, n(C) = 120; j: n(A) = 190, n(B) = 215, n(C) = 86; k: n(A) = 189, n(B) = 215, n(C) = 86; l: n(A) = 322, n(B) = 349, n(C) = 160; m: n(A) = 320, n(B) = 347, n(C) = 160; n: n(A) = 283, n(B) = 307, n(C) = 138; o: n(A) = 283, n(B) = 307, n(C) = 138. *p < 0.05 vs. group A. #p < 0.05 vs. group B.

acute cardiac injury (10.5% vs. 9.5% vs. 6.8%, p < 0.05) showed a decreasing trend among the three groups, although the differences were not significant. The complications and treatment for all patients are listed in Table 6.

3.4. Clinical classification and prognosis

More mild-moderate patients (36.1% vs. 37.2% vs. 54.7%, p < 0.05) were reported, and fewer severe patients (38.6% vs. 39.7% vs. 28%, p < 0.05) were shown in group C than in group A and B. In addition, the number of critical patients (25.3% vs. 23.2% vs. 17.4%, p < 0.05) gradually reduced among the three groups, although no significant differences were reported. The death rate was reported to show a decreasing trend among the three groups. Group C had a lower death rate (11.7% vs. 8.4% vs. 5.6%, p < 0.05) than Group A and B. However, no differences were found in other items. The clinical classification and prognosis for all patients are listed in Table 7.

4. Discussion

Our study suggested that the clinical characteristics and prognosis of patients with COVID-19 may have subtly changed with time in Wuhan. Before admission, fewer patients had fever in group C (i.e., in the later stage of the epidemic) than in the first and second groups. Patients in group C were more likely to have improved results of laboratory tests and lung CT, lower incidence of complications, more mild-moderate patients and lower death rate.

According to a recent publication [12], the prevention of COVID-19 could be divided into five phases. Among them, the second stage was from January 10 to January 22, 2020. This stage coincides with the Spring Festival, in which large-scale population movements have led to the widespread spread of COVID-19. The third stage was from January 23 to February 1, 2020. Wuhan government announced the “closure of the city”, and then adopted a series of mandatory measures, including wearing masks in public places and canceling all social gatherings. Due to limited medical resources, many patients or suspected patients were isolated at home. The fourth stage was from February 2 to February 16, 2020. With improvement in medical resources, the government implemented a policy of centralized quarantine and treatment of all confirmed and presumptive cases, those with fever or respiratory symptoms, and close contacts of confirmed cases in designated hospitals or facilities. In addition, we found that January 26 and February 1 are the two obvious time nodes shown in the distribution curve of number of inpatients per day in our cohort (Supplemental Fig. S1). And the distribution of each symptom in different phases showed a dynamic changes with time (Supplemental Fig. S2). Based on the information discussed above, in the present study, we divided these patients into the three groups according to the onset time of clinical symptoms, with January 25 and February 1 as the break point.

SARS-CoV-2 is rapidly spreading around the world, and COVID-19

Table 4
Inflammatory response and immunoreaction of COVID-19 patients on admission.

	Median (IQR)			
	ALL (n = 843)	Group A (n = 324)	Group B (n = 358)	Group C (n = 161)
Nonspecific inflammation index				
C-reactive protein, mg/L[a]	30.8 (5.4, 73.6)	26.8 (5.6, 77.5)	33.7 (6.1, 70.9)	31.0 (5.0, 70.7)
High-sensitivity C-reactive protein, mg/L[b]	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)
Serum amyloid protein, mg/L[c]	38.8 (5.0, 200.0)	74.1 (5.0, 236.5)	28.1 (5.0, 200.0)	13.1 (5.0, 126.8)
Erythrocyte sedimentation rate, mm/h[d]	55 (31, 71)	52 (30, 68)	57 (32, 92)	55 (36, 66)
Procalcitonin, ng/mL[e]	0.060 (0.036, 0.128)	0.056 (0.034, 0.129)	0.062 (0.036, 0.125)	0.060 (0.037, 0.130)
Cytokines[f]				
Interferon-γ, pg/mL	4.00 (2.69, 5.75)	4.00 (2.72, 6.86)	3.82 (2.57, 4.75)	4.53 (3.18, 6.11)
Interleukin 5, pg/mL[g]	2.24 (2.13, 2.35)	2.22 (2.13, 2.35)	2.31 (2.16, 2.40)	2.13 (2.12, 2.24)
Interleukin 6, pg/mL[h]	7.64 (2.91, 18.74)	7.78 (2.59, 15.59)	6.92 (3.67, 18.60)	7.24 (3.64, 26.26)
interleukin 10, pg/mL	5.72 (4.75, 7.40)	5.70 (4.73, 7.48)	5.75 (4.80, 7.51)	5.72 (4.75, 6.68)
Tumor necrosis factor, pg/mL	3.12 (2.76, 4.53)	3.06 (2.72, 4.44)	3.11 (2.82, 3.85)	3.66 (2.77, 4.60)
Humoral immunity[i]				
Complement 3, g/L	1.01 (0.87, 1.15)	1.01 (0.87, 1.14)	1.03 (0.87, 1.17)	1.00 (0.87, 1.14)
Complement 4, g/L	0.26 (0.19, 0.33)	0.24 (0.18, 0.32)	0.26 (0.20, 0.33)	0.27 (0.21, 0.35)*
Immunoglobulin A, g/L	2.36 (1.79, 3.01)	2.32 (1.78, 2.90)	2.38 (1.79, 3.12)	2.37 (1.79, 3.01)
Immunoglobulin E, IU/mL	47.1 (18.3, 130.0)	52.3 (18.3, 127.5)	45.3 (18.3, 136.0)	41.5 (19.1, 123.0)
Immunoglobulin G, g/L	11.9 (10.1, 14.1)	11.9 (10.2, 14.3)	11.9 (10.4, 14.2)	11.6 (9.8, 13.8)#
Immunoglobulin M, g/L	0.932 (0.683, 1.230)	0.971 (0.716, 1.260)	0.891 (0.671, 1.210)	0.958 (0.673, 1.260)
Cellular immunity[j]				
CD16 + 56, %	13.31 (8.69, 20.62)	13.28 (8.29, 21.23)	13.90 (8.91, 20.57)	12.28 (8.68, 20.25)
CD16 + 56 counts, No./μL	117 (74, 180)	117 (65, 192)	116 (77, 166)	117 (79, 205)
CD19, %	15.72 (11.53, 21.36)	16.12 (11.74, 21.90)	15.94 (11.68, 21.52)	15.09 (11.16, 19.68)
CD19 counts, No./μL	138.0 (91.6, 202.0)	140.0 (91.0, 195.8)	132.0 (85.3, 204.5)	140.0 (101.5, 215.0)
CD3, %	66.61 (56.60, 73.93)	64.98 (56.40, 72.93)	66.59 (56.22, 73.39)	67.96 (57.44, 75.87)
CD3 counts No./μL	593.0 (377.0, 902.5)	591.0 (323.0, 856.5)	583.5 (380.8, 870.0)	665.0 (453.0, 1026.0)*#
CD4, %	39.55 (31.66, 46.07)	38.64 (31.48, 45.86)	40.36 (32.16, 46.58)	39.70 (31.01, 46.29)
CD4 counts, No./μL	357.0 (217.0, 546.5)	343.5 (205.0, 519.5)	348.5 (211.3, 542.3)	380.0 (272.5, 598.5)
CD8, %	22.04 (15.83, 29.08)	22.56 (15.92, 29.26)	21.41 (15.96, 27.88)	23.42 (15.55, 29.47)
CD8 counts, No./μL	209.0 (112.0, 329.5)	216.0 (106.3, 319.5)	194.5 (113.0, 318.8)	229.0 (116.0, 366.0)#
CD4/CD8	1.78 (1.24, 2.69)	1.71 (1.23, 2.53)	1.86 (1.30, 2.85)	1.57 (1.21, 2.76)

The total number of patients with available data: a: n(A) = 310, n(B) = 339, n(C) = 152; b: n(A) = 309, n(B) = 335, n(C) = 153; c: n(A) = 66, n(B) = 63, n (C) = 38; d: n(A) = 37, n(B) = 32, n(C) = 18; e: n(A) = 283, n(B) = 300, n(C) = 123; f: n(A) = 70, n(B) = 66, n(C) = 25; g: n(A) = 18, n(B) = 19, n(C) = 6; h: n (A) = 144, n(B) = 150, n(C) = 56; i: n(A) = 271, n(B) = 303, n(C) = 143; j: n(A) = 286, n(B) = 310, n(C) = 143. * $p < 0.05$ vs. group A. # $p < 0.05$ vs. group B.

has been designated a global pandemic. SARS-CoV-2 has various transmission routes, mainly respiratory and contact transmission [11]. Previous reports revealed that outbreaks of SARS overwhelmed medical resources in a short time, resulting in longer intervals from the onset of symptoms to admission earlier in the epidemic of Hong Kong [13]. Progressive shortening of the onset-to-admission interval could be observed, especially at the later stage [14]. In addition, M Liu suggested that a shorter interval before clinical consultation was a protective factor for surviving SARS [15]. Consistent with previous studies, our study found that a shorter interval before doctor consultation was observed at the later stage of this epidemic, which was associated with a better prognosis. Several reasons may be responsible for the trend. More designated hospitals, venues newly converted into hospitals and a sufficient number of health workers through aid from other areas provided more than tens of thousands of beds for patients, and enforced quarantine was effective for helping to identify patients and control the outbreak. These interventions have been demonstrated to be highly beneficial for the treatment of patients [10,16,17].

Previous studies have shown that clinical manifestations of COVID-19 include fever, nonproductive cough, dyspnea, myalgia and fatigue [6,18]. Furthermore, COVID-19 rarely developed intestinal signs and symptoms (e.g., diarrhea), whereas approximately 20–25% of patients with MERS or SARS had diarrhea [6,19]. Similar to these reports, our study also showed that most patients presented with fever, nonproductive cough and dyspnea. Previous studies suggested that transmission characteristics may change with the evolution of viruses. Other researchers revealed that a novel mutation has been found in Europe, and initial symptoms may subtly change with time in Wuhan [8,9]. We analyzed clinical dynamics, suggesting that most of the initial symptoms of patients in Wuhan remained constant. However, group C had fewer patients with fever before admission. This phenomenon deserves further attention since it may increase doctors' difficulty in

Table 5
Initial pulmonary CT findings of COVID-19 patients.

No. (%) Characteristics of lung CT	All (n = 467)	Group A (n = 168)	Group B (n = 197)	Group C (n = 102)
Pneumonia	452(96.8%)	165(98.2%)	191 (97.0%)	96(94.1%)
Unilateral lung	60 (12.8%)	15 (8.9%)	23 (11.7%)	22 (21.6%)*#
Bilateral lung	392 (83.9%)	150 (89.3%)	168 (85.3%)	74 (72.5%)*#
Ground-glass opacity	361 (77.3%)	132 (78.6%)	151 (76.6%)	78(76.5%)
Paving stone/reticular/linear	127 (27.2%)	45 (26.8%)	59 (29.9%)	23 (22.5%)
Consolidation shadow	65 (13.9%)	23 (13.7%)	24 (12.2%)	18 (17.6%)
Air bronchogram	48 (10.3%)	20 (11.9%)	19 (9.6%)	9 (8.8%)

Abbreviation: CT: Computerized tomography. *$p < 0.05$ vs. group A. # $p < 0.05$ vs. group B.

Table 6
Complications and treatments of COVID-19 patients.

	ALL (n = 843)	Group A (n = 324)	Group B (n = 358)	Group C (n = 161)
Complications, No. (%)	129 (15.3%)	60 (18.5%)	51 (14.2%)	18 (11.2%)*
Shock	50 (5.9%)	21 (6.5%)	20 (5.6%)	9 (5.6%)
Acute cardiac injury	79 (9.4%)	34 (10.5%)	34 (9.5%)	11 (6.8%)
Acute renal injury	11 (1.3%)	6 (1.9%)	2 (0.6%)	3 (1.9%)
Acute liver injury	37 (4.4%)	18 (5.6%)	12 (3.4%)	7 (4.3%)
Only one complication	94 (11.2%)	46 (14.2%)	37 (10.3%)	11 (6.8%)*
≥2 complications	35 (4.2%)	14 (4.3%)	12 (3.4%)	7 (4.3%)
Admission to ICU, No. (%)	41 (4.9%)	19 (5.9%)	17 (4.7%)	5 (3.1%)
Oxygen therapy, No. (%)				
Nasal catheter oxygen inhalation	553 (65.6%)	210 (64.8%)	235 (65.6%)	108 (67.1%)
Mask oxygen inhalation	257 (30.5%)	98 (30.2%)	120 (33.5%)	39 (24.2%)#
HFBHTI	63 (7.5%)	22 (6.8%)	28 (7.8%)	13 (8.1%)
Non-invasive mechanical ventilation	105 (12.5%)	45 (13.9%)	43 (12%)	17 (10.6%)
Invasive mechanical ventilation	23 (2.7%)	10 (3.1%)	9 (2.5%)	4 (2.5%)
Medical treatment, No. (%)				
Antiviral treatment	797 (94.5%)	294 (90.7%)	346 (96.6%)*	157 (97.5%)*
Antibiotic treatment	662 (78.5%)	245 (75.6%)	287 (80.2%)	130 (80.7%)
Antifungal treatment	12 (1.4%)	3 (0.9%)	6 (1.7%)	3 (1.9%)
Intravenous glucocorticoids	391 (46.4%)	151 (46.6%)	165 (46.1%)	75 (46.6%)
Immunoglobulin therapy	430(51.0%)	175 (54%)	181 (50.6%)	74 (46%)
Special treatment, No. (%)				
CRRT	8 (1.0%)	3 (0.9%)	5 (1.4%)	0 (0%)
ECMO	2 (0.2%)	1 (0.3%)	1 (0.3%)	0 (0%)
ALSS	9 (1.1%)	2 (0.6%)	5 (1.4%)	2 (1.2%)

Abbreviation: ALSS: artificial liver support system; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; IQR: interquartile range. * $p < 0.05$ vs. group A. # $p < 0.05$ vs. group B.

distinguishing suspected patients based on fever.

F Zhou suggested that older age, higher Sequential Organ Failure Assessment (SOFA) score and D-dimer levels greater than 1 μg/ml were associated with poor prognosis for patients with COVID-19 early in Wuhan [20]. Another literature report found that older age was an obvious risk factor for the development of ARDS and death [21]. In addition, patients with one comorbidity had poorer outcomes than those without, and patients with more than one comorbidity were associated with greater risk for the cumulative endpoints than those with only one comorbidity [22]. In our study, group C had more patients aged younger than 45 years and fewer patients with more than one comorbidity, both of which were also associated with a better prognosis. The reason for the higher proportion of young patients in group C may be associated with the policy of Chinese government [12]. More designated hospitals, venues newly converted into hospitals and a sufficient number of health workers from other areas provided more than tens of thousands of beds for patients, and enforced quarantine was effective for helping to identify patients earlier. With sufficient and timely medical treatment, the onset-to-admission interval was shortened and more young patients with less comorbidities were admitted into the hospital. With shortened onset-to-admission interval, the laboratory tests and CT manifestations were improved. All these factors may positively contribute to the improved prognosis at the later stage of the epidemic.

The pathophysiology of the unusually high pathogenicity for SARS-CoV-2 is not completely understood. Lymphocytopenia is a prominent feature of COVID-19 because targeted invasion by SARS-CoV-2 particles damages the cytoplasmic component of lymphocytes and causes their destruction. Additionally, the severity of lymphocytopenia is closely related to the severity of SARS-CoV-2 infection [23]. ICU patients had higher white blood cell counts, neutrophil counts, LDH levels, lactic acid levels and d-dimer levels than non-ICU patients [7]. In addition, lactic acid accumulation and D-dimer greater than 1 μg/ml may be associated with poor prognosis for patients with COVID-19 [20,24]. In this retrospective study, we found that more than half of patients among all three groups had lymphopenia, although group C showed higher lymphocyte counts than the other two groups. In addition, the white blood cell count, neutrophil count, lactic acid level and D-dimer level were lower in group C. These results may be responsible for the better outcome of patients in group C. In addition, CD8 and CD3 counts were higher in patients with a later onset date. CD8 exhaustion was significantly associated with the development of COVID-19 [25], which suggested that higher CD8 counts were beneficial for the recovery of patients. Similarly, we found improved CT manifestations in group C. A previous study suggested that worse CT manifestations were shown in severe/critical patients with COVID-19 than in mild and moderate

Table 7
Clinical classification and prognosis of COVID-19 patients.

	ALL(n = 843)	Group A (n = 324)	Group B (n = 358)	Group C (n = 161)
Clinical classification, No. (%)				
Mild-Moderate	404 (47.9%)	146 (45.1%)	163 (45.5%)	95 (59.0%)*#
Severe	291 (34.5%)	112 (34.6%)	134 (37.4%)	45 (28.0%)
Critical	148 (17.6%)	66 (20.4%)	61 (17.0%)	21 (13.0%)
Prognosis, No. (%) or Median (IQR)				
Death	77 (9.1%)	38 (11.7%)	30 (8.4%)	9 (5.6%)*
Onset of disease to death, d	11 (10, 13)	10.5 (9.25, 13)	12 (10, 14)	9 (7, 12)
From hospitalization to death, d	5 (3, 8)	5 (3, 7)	5.5 (3, 8)	7 (3, 9.5)
Discharge or Transfer to the isolation point	83 (9.8%)	26 (8.0%)	38 (10.6%)	19 (11.8%)
Staying in hospital	683 (81.0%)	260 (80.2%)	290 (81.0%)	133 (82.6%)

Abbreviation: d: day; IQR: interquartile range. * $p < 0.05$ vs. group A. # $p < 0.05$ vs. group B.

patients [26]. Therefore, improved CT manifestations may subtly contribute to the improved outcomes of patients at the later stage of the outbreak in Wuhan.

It was initially considered that the lung is the most commonly damaged organ by SARS-CoV-2 infection since human airway epithelia express the angiotensin converting enzyme 2 (ACE2) receptor, a host cell receptor for SARS-CoV-2 infection [27]. However, increasing clinical cases indicated cardiac, renal and even digestive organ damage in patients with COVID-19, which was consistent with the findings that kidney, colon and other tissues also express the ACE2 receptor [28,29]. Similar to these reports, our study also showed that a considerable number of patients developed complications, including shock, acute cardiac injury, acute renal injury and acute liver injury. Interestingly, the incidence of complications was significantly lower in group C, suggesting that the condition of the latter group may be less serious.

The clinical spectrum of COVID-19 ranges from mild to critically ill cases. In this retrospective study, we found that group C had more mild-moderate patients and fewer severe patients. In addition, the death rate in group C was 5.6%, which was significantly lower than that in group A (11.7%) and group B (8.4%). These results suggested that the mortality of patients with COVID-19 was restrained in Wuhan. An increasing number of younger patients, fewer patients with more than one comorbidity, shortened time intervals before consulting doctors, improved laboratory tests, recovered CD8 counts, improved CT manifestations and fewer complications may contribute to the improved prognosis at the later stage of the epidemic in Wuhan.

This study has several limitations. First, this study was a retrospective study in a single center. Second, we only analyzed the first laboratory results after admission and lacked dynamic observations of these results. Finally, since the median interval from admission to death was 6 days in the preliminary study of the overall population, we observed the outcomes of patients within 12 days of hospitalization among the three groups. However, a longer observation time will be needed in future studies.

5. Conclusion

The clinical characteristics and prognosis of patients with COVID-19 subtly changed with time between Jan 22, 2020 and Feb 14, 2020 in Wuhan. An improved prognosis was observed at the later stage of the epidemic.

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Author contribution

MLW, JSZ, ZW, DY, JFL and JW designed study, collected and analyzed data, and wrote manuscript. YX, JY, MXL, MMZ, ZL, WP, MLL and DL collected and reviewed clinical, laboratory, and radiological data. YX and JSZ performed statistical analysis. BS, HH, PAZ, JG and JW reviewed, interpreted, and checked clinical data. JW edited manuscript, and supervised the study.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2020.06.051.

References

[1] J. Liu, X. Zheng, Q. Tong, W. Li, B. Wang, K. Sutter, M. Trilling, M. Lu, U. Dittmer, D. Yang, Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV, J. Med. Virol. 92 (5) (2020) 491–494.

[2] Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, R. Ren, K.S.M. Leung, E.H.Y. Lau, J.Y. Wong, X. Xing, N. Xiang, Y. Wu, C. Li, Q. Chen, D. Li, T. Liu, J. Zhao, M. Liu, W. Tu, C. Chen, L. Jin, R. Yang, Q. Wang, S. Zhou, R. Wang, H. Liu, Y. Luo, Y. Liu, G. Shao, H. Li, Z. Tao, Y. Yang, Z. Deng, B. Liu, Z. Ma, Y. Zhang, G. Shi, T.T.Y. Lam, J.T. Wu, G.F. Gao, B.J. Cowling, B. Yang, G.M. Leung, Z. Feng, Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia, N. Engl. J. Med. 382 (13) (2020) 1199–1207.

[3] R. Lu, X. Zhao, J. Li, P. Niu, B. Yang, H. Wu, W. Wang, H. Song, B. Huang, N. Zhu, Y. Bi, X. Ma, F. Zhan, L. Wang, T. Hu, H. Zhou, Z. Hu, W. Zhou, L. Zhao, J. Chen, Y. Meng, J. Wang, Y. Lin, J. Yuan, Z. Xie, J. Ma, W.J. Liu, D. Wang, W. Xu, E.C. Holmes, G.F. Gao, G. Wu, W. Chen, W. Shi, W. Tan, Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, Lancet 395 (10224) (2020) 565–574.

[4] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, X. Zhao, B. Huang, W. Shi, R. Lu, P. Niu, F. Zhan, X. Ma, D. Wang, W. Xu, G. Wu, G.F. Gao, W. Tan, A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (8) (2020) 727–733.

[5] W.H. Organization, WHO Director-General s remarks at the media briefing on 2019-nCoV on 11 February 2020, 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020 (accessed February 23 2020).

[6] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506.

[7] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang, Z. Peng, Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, Jama 323 (11) (2020) 1061–1069.

[8] Z. Chen, J. Hu, Z. Zhang, S. Jiang, T. Wang, Z. Shi, Z. Zhang, Caution: The clinical characteristics of COVID-19 patients at admission are changing, medRxiv (2020) 2020.03.03.20030833.

[9] M. Wang, M. Li, R. Ren, A. Brave, S.v.d. Werf, E.-Q. Chen, Z. Zong, W. Li, B. Ying, International expansion of a novel SARS-CoV-2 mutant, medRxiv (2020) 2020.03.15.20035204.

[10] Z. Zhang, W. Yao, Y. Wang, C. Long, X. Fu, Wuhan and Hubei COVID-19 mortality analysis reveals the critical role of timely supply of medical resources, medRxiv (2020) 2020.03.13.20035410.

[11] N.H.C.o.t.P.s.R.o. China, Diagnosis and treatment of novel coronavirus infected pneumonia (trial 6th edition), 2020. http://www.nhc.gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8aefc2.shtml.

[12] A. Pan, L. Liu, C. Wang, H. Guo, X. Hao, Q. Wang, J. Huang, N. He, H. Yu, X. Lin, S. Wei, T. Wu, Association of public health interventions with the epidemiology of the COVID-19 outbreak in Wuhan, China, JAMA 323 (19) (2020) 1–9.

[13] C.A. Donnelly, A.C. Ghani, G.M. Leung, A.J. Hedley, C. Fraser, S. Riley, L.J. Abu-Raddad, L.M. Ho, T.Q. Thach, P. Chau, K.P. Chan, T.H. Lam, L.Y. Tse, T. Tsang, S.H. Liu, J.H. Kong, E.M. Lau, N.M. Ferguson, R.M. Anderson, Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong, Lancet 361 (9371) (2003) 1761–1766.

[14] E.H. Lau, C.A. Hsiung, B.J. Cowling, C.H. Chen, L.M. Ho, T. Tsang, C.W. Chang, C.A. Donnelly, G.M. Leung, A comparative epidemiologic analysis of SARS in Hong Kong, Beijing and Taiwan, BMC Infect. Dis. 10 (2010) 50.

[15] M. Liu, W.N. Liang, Q. Chen, X.Q. Xie, J. Wu, X. He, Z.J. Liu, Risk factors for SARS-related deaths in 2003, Beijing, Biomed. Environ. Sci. 19 (5) (2006) 336–339.

[16] W.H. Organization, Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), 2020. https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-finalreport.pdf.

[17] X. Zhou, Z. Wu, R. Yu, S. Cao, W. Fang, Z. Jiang, F. Yuan, C. Yan, D. Chen, Modelling-based evaluation of the effect of quarantine control by the Chinese government in the coronavirus disease 2019 outbreak, medRxiv (2020) 2020.03.03.20030445.

[18] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang, L. Zhang, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (10223) (2020) 507–513.

[19] A. Assiri, J.A. Al-Tawfiq, A.A. Al-Rabeeah, F.A. Al-Rabiah, S. Al-Hajjar, A. Al-Barrak, H. Flemban, W.N. Al-Nassir, H.H. Balkhy, R.F. Al-Hakeem, H.Q. Makhdoom, A.I. Zumla, Z.A. Memish, Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study, Lancet Infect. Dis. 13 (9) (2013) 752–761.

[20] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, J. Xiang, Y. Wang, B. Song, X. Gu, L. Guan, Y. Wei, H. Li, X. Wu, J. Xu, S. Tu, Y. Zhang, H. Chen, B. Cao, Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet 395 (10229) (2020) 1054–1062.

[21] C. Wu, X. Chen, Y. Cai, J. Xia, X. Zhou, S. Xu, H. Huang, L. Zhang, X. Zhou, C. Du, Y. Zhang, J. Song, S. Wang, Y. Chao, Z. Yang, J. Xu, X. Zhou, D. Chen, W. Xiong, L. Xu, F. Zhou, J. Jiang, C. Bai, J. Zheng, Y. Song, Risk factors associated with acute

respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China, JAMA Intern. Med. (2020).
[22] W.J. Guan, W.H. Liang, Y. Zhao, H.R. Liang, Z.S. Chen, Y.M. Li, X.Q. Liu, R.C. Chen, C.L. Tang, T. Wang, C.Q. Ou, L. Li, P.Y. Chen, L. Sang, W. Wang, J.F. Li, C.C. Li, L.M. Ou, B. Cheng, S. Xiong, Z.Y. Ni, J. Xiang, Y. Hu, L. Liu, H. Shan, C.L. Lei, Y.X. Peng, L. Wei, Y. Liu, Y.H. Hu, P. Peng, J.M. Wang, J.Y. Liu, Z. Chen, G. Li, Z.J. Zheng, S.Q. Qiu, J. Luo, C.J. Ye, S.Y. Zhu, L.L. Cheng, F. Ye, S.Y. Li, J.P. Zheng, N.F. Zhang, N.S. Zhong, J.X. He, Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis, Eur. Respir. J. 55 (5) (2020).
[23] X. Yang, Y. Yu, J. Xu, H. Shu, J. Xia, H. Liu, Y. Wu, L. Zhang, Z. Yu, M. Fang, T. Yu, Y. Wang, S. Pan, X. Zou, S. Yuan, Y. Shang, Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study, Lancet Respir. Med. 8 (5) (2020) 475–481.
[24] Y.D. Peng, K. Meng, H.Q. Guan, L. Leng, R.R. Zhu, B.Y. Wang, M.A. He, L.X. Cheng, K. Huang, Q.T. Zeng, Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV, Zhonghua Xin Xue Guan Bing Za Zhi 48 (2020) E004.
[25] P. Yang, Y. Ding, Z. Xu, R. Pu, P. Li, J. Yan, J. Liu, F. Meng, L. Huang, L. Shi, T. Jiang, E. Qin, M. Zhao, D. Zhang, P. Zhao, L. Yu, Z. Wang, Z. Hong, Z. Xiao, Q. Xi, D. Zhao, P. Yu, C. Zhu, Z. Chen, S. Zhang, J. Ji, G. Cao, F. Wang, Epidemiological and clinical features of COVID-19 patients with and without pneumonia in Beijing, China, medRxiv (2020) 2020.02.28.20028068.
[26] K. Li, J. Wu, F. Wu, D. Guo, L. Chen, Z. Fang, C. Li, The clinical and chest CT features associated with severe and critical COVID-19 pneumonia, Invest. Radiol. 55 (6) (2020) 327–331.
[27] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, S. Liu, P. Zhao, H. Liu, L. Zhu, Y. Tai, C. Bai, T. Gao, J. Song, P. Xia, J. Dong, J. Zhao, F.S. Wang, Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet Respir. Med. 8 (4) (2020) 420–422.
[28] W.-j. Guan, Z.-y. Ni, Y. Hu, W.-h. Liang, C.-q. Ou, J.-x. He, L. Liu, H. Shan, C.-l. Lei, D.S.C. Hui, B. Du, L.-j. Li, G. Zeng, K.-Y. Yuen, R.-c. Chen, C.-l. Tang, T. Wang, P.-y. Chen, J. Xiang, S.-y. Li, J.-l. Wang, Z.-j. Liang, Y.-x. Peng, L. Wei, Y. Liu, Y.-h. Hu, P. Peng, J.-m. Wang, J.-y. Liu, Z. Chen, G. Li, Z.-j. Zheng, S.-q. Qiu, J. Luo, C.-j. Ye, S.-y. Zhu, N.-s. Zhong, Clinical characteristics of 2019 novel coronavirus infection in China, medRxiv (2020) 2020.02.06.20020974.
[29] J. Wang, S. Zhao, M. Liu, Z. Zhao, Y. Xu, P. Wang, M. Lin, Y. Xu, B. Huang, X. Zuo, Z. Chen, F. Bai, J. Cui, A.M. Lew, J. Zhao, Y. Zhang, H. Luo, Y. Zhang, ACE2 expression by colonic epithelial cells is associated with viral infection, immunity and energy metabolism, medRxiv (2020) 2020.02.05.20020545.