Original Article

An analytical study of drug utilization, disease progression, and adverse events among 165 COVID-19 patients

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Background: The coronavirus disease 2019 (COVID-19) epidemic has lasted for nearly 4 months by this study was conducted. We aimed to describe drug utilization, disease progression, and adverse drug events of COVID-19.

Methods: A retrospective, single-center case series study enrolled 165 consecutive hospitalized COVID-19 patients who were followed up until March 25, 2020, from a designated hospital in Wuhan. Patients were grouped by a baseline degree of severity: non-severe and severe. An analytical study of drug utilization, disease progression, and adverse events (AEs) of COVID-19 was conducted.

Results: Of the 165 COVID-19 cases, antivirals, antibacterials, glucocorticoids, and traditional Chinese medicine (TCM) were administered to 92.7%, 98.8%, 68.5%, and 55.2% of patients, respectively. The total kinds of drugs administered to the severe subgroup [26, interquartile range (IQR) 18–39] were 11 more than the non-severe subgroup (15, IQR 10–24), regardless of comorbidities. The 2 most common combinations of medications in the 165 cases were 'antiviral therapy + glucocorticoids + TCM' (81, 49.1%) and 'antiviral therapy + glucocorticoids' (23, 13.9%). Compared with non-severe cases, severe cases received more glucocorticoids (88.5% *vs.* 66.2%, P=0.02), but less TCM (50.0% *vs.* 63.3%, P=0.20), and suffered a higher percentage of death (34.6% *vs.* 7.2%, P=0.001). At the end of the follow-up, 130 (78.8%) patients had been discharged, and 24 (14.5%) died. There were 13 patients (7.9%) who had elevated liver enzymes, and 49 patients (29.7%) presented with worsening kidney function during the follow-up.

Conclusions: Of the 165 COVID-19 patients, the fatality rate remained high (14.5%). Drug utilization for COVID-19 was diverse and generally complied with the existing guidelines. Combination regimens containing antiviral drugs might be beneficial to assist COVID-19 recovery. Additionally, liver and kidney AEs should not be ignored.

Keywords: Novel coronavirus disease (COVID-19); drug utilization; disease progression; fatality; adverse events (AEs)

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Introduction

The outbreak of coronavirus disease 2019 (COVID-19) has quickly swept across the world (1,2), and has been declared a Public Health Emergency of International Concern (PHEIC) since January 30, 2020 (3,4). As of April 20, 2020, 210 countries and territories worldwide have reported a total of 2,481,026 confirmed cases and a death toll of 170,423. This situation already poses a serious global public health risk.

In the early stages of the outbreak, despite facing many challenges in understanding and treating COVID-19, especially a lack of specific antiviral agents, attempts at medication strategies had already been introduced into clinical practice by Chinese front-line physicians (5-9). To date, the 7th updated version of the official diagnosis and treatment guidelines has already been published (10-14), and some achievements have been made in improving case fatality and enhancing the cure rate of COVID-19 patients. However, some concerns, including medication choices and combination and safety issues, have inevitably been raised (9,15-18). Previous studies have only described general epidemiological findings, clinical presentation, and clinical outcomes of COVID-19 patients (5-9,19-22). Furthermore, few of these studies have systematically characterized the drug utilization of COVID-19 patients. Therefore, our study's objectives were to give a full description of drug utilization, disease progression, and adverse drug events (ADEs) of COVID-19. We present the following article following the MDAR reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4960).

Methods

Participants and data sources

This retrospective, single-center case series study enrolled 165 consecutive COVID-19 patients initially hospitalized at Zhongnan Hospital of Wuhan University in Wuhan, China, from December 19, 2019, to February 2, 2020. All patients were followed up to March 25, 2020, and were ≥18 years old and not diagnosed with bacterial pneumonia. Zhongnan Hospital is one of the major tertiary teaching hospitals in Wuhan, Hubei Province, and has been responsible for treating COVID-19 patients assigned by the government. According to the World Health Organization (WHO) interim guidance, all patients enrolled in this study were confirmed to be COVID-19 positive by viral test on admission (WHO) interim guidance (23,24).

The participants' predefined information was extracted from electronic medical records (EMR), including demographics, treatment, and prognosis. A trained team of physicians and clinical pharmacists reviewed all data for accuracy and completeness. The research database was composed of 3 parts: (I) baseline characteristics, including demographics, COVID-19 contact history, underlying comorbidities; (II) diagnosis and treatment, including symptoms and signs, laboratory markers, chest computed tomographic (CT) scans, and medication (i.e., dosage, initial, and prescription and discontinuation date); (III) prognosis (death, recovery, or remained in hospital).

Medications and outcomes

We mainly focused on 9 classes of treatments according to the different versions of the guidelines for diagnosis and treatment of COVID-19 (Table S1): antivirals for systemic use [Anatomical Therapeutic Chemical (ATC) classification codes starting with J05], antibacterials for systemic use (J01), glucocorticoids for systemic use (H02AB), antimycotics for systemic use (J02), traditional Chinese medicines (TCM, identified by using drug name), general nutrients (V06), vasoactive drugs (C01DA, C01CA, and C04AB01), intestinal microecological regulators (A07F), and immunoglobulins (J06BA). The total kinds of medications (according to generic names) used per person during hospitalization were also calculated—each prescription interval accumulated the total treatment duration for specific classes/kinds of drugs.

According to the guidelines, patient baseline condition severity was classified into 4 levels: mild, general, severe, and critically severe (12). The first 2 levels were further combined as the non-severe subgroup, and the latter 2 as the severe subgroup. Disease exacerbation was defined as the measure of disease condition getting worse at any time after admission.

Blood samples were tested for creatinine (reference value <90 μmol/L), alanine aminotransferase (ALT, reference value <45 U/L), and aspartate aminotransferase (AST, reference value <40 U/L). Urine samples were tested for albumin (normal sign with "negative"). The creatinine result was used in an equation with the patient's age, race, and sex to calculate the glomerular filtration rate (GFR, normal range of ≥90 mL/min/1.73 m^2) (25). Laboratory abnormalities were used to define elevated serum aminotransferase levels and impaired renal function.

Statistical analysis

We first compared the baseline characteristics (including

age, gender, occupation, etc.), drug utilization (including types of drugs, combination patterns, the number of the medications, total treatment duration, dosage, etc.), and potential adverse events (AEs) between the non-severe and severe subgroups. Furthermore, basic characteristics were compared between patients that had ever used or never used specific classes/kinds of drugs to explore the potentially influential factors for drug selection.

Frequency and percentages were described for categorical variables, and χ^2 or Fisher's exact test was used for comparing the proportions in different subgroups. Median and interquartile range (IQR) were reported for the count and continuous variables, and the two-sample median test (26) was used for comparing medians of different subgroups. A two-sided P value of less than 0.05 was considered statistically significant. All analyses were performed using the SAS software (version 9.4) and R software (version 3.6.2).

The study was conducted following the Declaration of Helsinki (as revised in 2013). The Institutional Ethics Board of Zhongnan Hospital of Wuhan University approved this study (No. 2020014). Written informed consent was waived for emerging infectious diseases.

Results

Baseline features

The study included 165 COVID-19 patients. The median age was 55 years (IQR, 42–66; range, 22–96 years), and 84 (50.9%) were men. Of these patients, 26 (15.8%) were in the severe subgroup, and 139 (84.2%) were in the non-severe subgroup at admission. Compared with the non-severe subgroup (*Table 1*), the severe patients were approximately 13 years older, with a higher proportion of comorbidities (84.6% *vs.* 44.6%). The most common comorbidities were hypertension (24.8%), cardiovascular disease (9.7%), diabetes (7.3%), and cancer (4.8%). A nonsignificant difference was detected in either sex, contact history, or other clinical features between the 2 groups, except that the severe subgroup had more frequent onsets of dyspnea or shortness of breath (23.1% *vs.* 4.3% for the non-severe subgroup) (Table S2).

Overall drug utilization

Among the 165 cases, antivirals (75.8% for oseltamivir, 43.0% for α-interferon, 13.9% for lopinavir/ritonavir), antibacterials, glucocorticoids, general nutrients, and TCM were received by 92.7%, 98.8%, 69.7%, 77.0%, and 61.2% of patients, respectively (*Table 2*). The combinations of the medications were quite diverse (Figure S1), and the top 4 medication combinations were antivirals combined with glucocorticoids and TCM (81, 49.1%), antivirals combined with glucocorticoids (23, 13.9%), only antivirals (27, 16.4%), and antivirals combined with TCM (22, 13.3%) without considering other coexisting medications (Table S3). A median of 17 (IQR, 10–29) kinds of drugs were prescribed to each patient. Patients with and without comorbidities took a median of 21 (IQR, 15–40) and 12 (IQR, 8–19) kinds of drugs, respectively, and the difference was statistically significant (P<0.001) (*Figure 1A* and Table S3). Most patients received only 1 kind of antiviral drug (IQR, 1–2), and only 5 patients took more than 3 kinds of antiviral drugs during hospitalization.

The median duration of antivirals was 8 days (IQR, 6–12), with 30.9% of patients taking antivirals longer than 10 days. Antibacterials and glucocorticoids were treated with a median of 12 days (IQR, 9–18) and 7 days (IQR, 4–12), respectively (*Table 2*). Regarding the doses of antivirals and glucocorticoids, the single-dose administrations mostly followed the guidelines (Table S4). Also, patients with comorbidities were less likely to receive TCM, whereas patients who were older or with more comorbidities were more likely to be administered other medications (Tables S5-S12).

Drug utilization differences between severity groups

Compared with non-severe cases, more severe cases received glucocorticoids (88.5% *vs.* 66.2%, P=0.02) and vasoactive drugs (50.0% *vs.* 19.4%, P<0.001), but received less TCM (50.0% *vs.* 63.3%, P=0.20). The total kinds of drugs administered to the severe subgroup (27, IQR 18–41) was 12 more than the non-severe subgroup (15, IQR 10–27) regardless of comorbidities (*Figure 1A*, P<0.001). Severe cases were more likely to take a higher single dose (5 million U) of α-interferon, a longer glucocorticoid duration, or a shorter immunoglobulin treatment. All other features, in terms of duration or single-dose administrations, were not significantly different between the 2 severity groups (*Table 2* and Table S4).

Patterns of disease progression

By March 25, 130 (78.8%) of the 165 patients had been discharged. Of all 165 patients, 24 (14.5%) patients had died, while the rest of the patients were still in the hospital

Table 1 Baseline characteristics of 165 patients with coronavirus disease 2019 (COVID-19)

Characteristics	All patients (n=165)	Disease severity[a]		P value
		Non-severe group (n=139)	Severe group (n=26)	
Age, years, median [IQR]	55 [42–66]	53 [37–65]	66 [57–76]	0.003
Groups				0.002
15–49 years	59 (35.8)	56 (40.3)	3 (11.5)	
50–64 years	55 (33.3)	47 (33.8)	8 (30.8)	
≥65 years	51 (30.9)	36 (25.9)	15 (57.7)	
Sex				0.451
Female	81 (49.1)	70 (50.4)	11 (42.3)	
Male	84 (50.9)	69 (49.6)	15 (57.7)	
Occupation				0.023
Retired	58 (35.2)	44 (31.7)	14 (53.8)	
Medical staff	32 (19.4)	32 (23.0)	0 (0.0)	
Others	50 (30.3)	41 (29.5)	9 (34.6)	
Unclear	25 (15.2)	22 (15.8)	3 (11.5)	
Has clear contact history				0.772
Yes	27 (16.4)	22 (15.8)	5 (19.2)	
No	138 (83.6)	117 (84.2)	21 (80.8)	
Comorbidities				
Any	84 (50.9)	62 (44.6)	22 (84.6)	<0.001
Hypertension	41 (24.8)	28 (20.1)	13 (50.0)	0.001
Cardiovascular disease	16 (9.7)	11 (7.9)	5 (19.2)	0.139
Diabetes	12 (7.3)	8 (5.8)	4 (15.4)	0.099
Cancer	8 (4.8)	6 (4.3)	2 (7.7)	0.613
Cerebrovascular disease	6 (3.6)	6 (4.3)	0 (0.0)	0.591
Chronic obstructive pulmonary disease	3 (1.8)	2 (1.4)	1 (3.8)	0.404
Chronic kidney disease	5 (3.0)	3 (2.2)	2 (7.7)	0.177
Chronic liver disease	3 (1.8)	2 (1.4)	1 (3.8)	0.404
HIV infection	2 (1.2)	2 (1.4)	0 (0.0)	>0.9999
HBV infection	4 (2.4)	4 (2.9)	0 (0.0)	>0.9999
Others	21 (12.7)	16 (11.5)	5 (19.2)	0.333
No. of comorbidities	1 [0–2]	0 [0–2]	2 [1–3]	<0.001

Data are presented as no. (%) or median [IQR]. [a], the patient's baseline condition was classified into 4 levels according to the guidelines: mild, general, severe, and critically severe, respectively. The first 2 levels were further classified as the non-severe subgroup, and the latter 2 as the severe subgroup. HIV, human immunodeficiency virus; HBV, hepatitis B virus; IQR, interquartile range.

Table 2 Drug utilization and their duration for 165 patients with coronavirus disease 2019 (COVID-19)

Drugs	Administering medications				Medication duration, days[b]			
	All patients (n=165)	Baseline disease severity[a]		P value	Patients used (n=165)	Baseline disease severity[a]		P value
		Non-severe group (n=139)	Severe group (n=26)			Non-severe group (n=139)	Severe group (n=26)	
Antivirals	153 (92.7)	129 (92.8)	24 (92.3)	>0.9999	8 [6–12]	8 [6–12]	8 [5–11]	0.787
α-interferon	71 (43.0)	58 (41.7)	13 (50.0)	0.434	8 [5–11]	9 [5–12]	6 [5–10]	0.379
Lopinavir/ritonavir	23 (13.9)	16 (11.5)	7 (26.9)	0.059	6 [5–9]	8 [6–9]	5 [4–9]	0.232
Ribavirin	3 (1.8)	2 (1.4)	1 (3.8)	0.404	2 [1–2]	2 [1–2]	2 [2–2]	0.480
Arbidol	14 (8.5)	14 (10.1)	0 (0.0)	0.129	1 [1–1]	1 [1–1]	–	NA
Oseltamivir	125 (75.8)	104 (74.8)	21 (80.8)	0.516	6 [4–8]	6 [4–8]	5 [4–7]	0.211
Others	7 (4.2)	7 (5.0)	0 (0.0)	0.598	6 [6–17]	6 [6–17]	–	NA
Antibacterials	163 (98.8)	137 (98.6)	26 (100.0)	1.000	12 [9–18]	12 [9–18]	15 [10–21]	0.189
Moxifloxacin	153 (92.7)	127 (91.4)	26 (100.0)	0.2167	10 [6–14]	9 [6–14]	10 [6–15]	0.7169
Ceftriaxone-tazobactam	63 (38.2)	52 (37.4)	11 (42.3)	0.63708	4 [3–7]	4 [3–7]	4 [2–7]	0.8605
Cefoperazone-tazobactam	34 (20.6)	30 (21.6)	4 (15.4)	0.47327	5 [4–8]	5 [4–8]	8 [4–11]	0.2705
Cefoperazone-sulbactam	33 (20.0)	26 (18.7)	7 (26.9)	0.33629	8 [5–16]	6 [5–16]	12 [2–17]	0.6111
Levofloxacin	33 (20.0)	29 (20.9)	4 (15.4)	0.52151	4 [2–9]	3 [2–9]	5 [3–9]	0.3716
Meropenem	31 (18.8)	26 (18.7)	5 (19.2)	>0.9999	9 [5–13]	9 [5–13]	9 [4–10]	0.6869
Amoxicillin-flucloxacillin	28 (17.0)	23 (16.5)	5 (19.2)	0.7768	5 [3–8]	5 [3–9]	4 [4–6]	0.6105
Biapenem	20 (12.1)	13 (9.4)	7 (26.9)	0.02	4 [2–9]	4 [2–9]	4 [2–8]	0.87
Piperacillin-tazobactam	20 (12.1)	11 (7.9)	9 (34.6)	0.0008	5 [3–10]	6 [2–11]	4 [3–8]	0.1888
Imipenem-cilastatin	18 (10.9)	13 (9.4)	5 (19.2)	0.1668	6 [3–9]	7 [5–9]	5 [3–5]	0.125
Cefminox	15 (9.1)	13 (9.4)	2 (7.7)	>0.9999	2 [1–5]	2 [1–3]	4 [2–5]	0.9219
Linezolid	13 (7.9)	10 (7.2)	3 (11.5)	0.4335	9 [5–11]	9 [5–11]	7 [1–14]	0.5839
All other antibacterials	46 (27.9)	36 (25.9)	10 (38.5)	0.18981	5 [1–9]	5 [1–9]	5 [2–15]	>0.9999
Glucocorticoids	115 (69.7)	92 (66.2)	23 (88.5)	0.023	7 [4–12]	6 [3–11]	9 [6–15]	0.020
Antimycotics	30 (18.2)	26 (18.7)	4 (15.4)	0.789	10 [6–14]	10 [6–14]	11 [4–24]	>0.9999
General nutrients	127 (77.0)	104 (74.8)	23 (88.5)	0.129	7 [3–13]	7 [3–12]	11 [4–15]	0.099
Traditional Chinese medicine	101 (61.2)	88 (63.3)	13 (50.0)	0.201	4 [2–11]	5 [2–13]	3 [2–6]	0.396
Vasoactive drugs	40 (24.2)	27 (19.4)	13 (50.0)	0.001	4 [2–10]	3 [1–10]	6 [3–8]	0.494
Intestinal microecological regulators	32 (19.4)	27 (19.4)	5 (19.2)	0.982	6 [2–14]	5 [1–13]	6 [4–16]	0.632
Immunoglobulins	28 (17.0)	22 (15.8)	6 (23.1)	0.395	6 [4–8]	7 [4–8]	5 [4–7]	0.348

Data are presented as no. (%) or median [IQR]. Medications include antivirals [Anatomical Therapeutic Chemical (ATC) classification codes starting with J05], antibacterials (J01), glucocorticoids (H02AB), antimycotics (J02), general nutrients (V06), traditional Chinese medicine (TCM, identified using drug name), vasoactive drugs (C01DA, C01CA, C04AB01), intestinal microecological regulators (A07F), and immunoglobulins (J06BA). [a], the patient's baseline condition was classified into 4 levels according to the guidelines: mild, general, severe, and critically severe, respectively. The first 2 levels were further classified as the non-severe subgroup, and the latter 2 as the severe subgroup. [b], the total treatment duration for specific classes/kinds of drugs was accumulated by each prescription interval. "–" means that none of severe patients were treated with that class of medication. NA, not applicable; IQR, interquartile range.

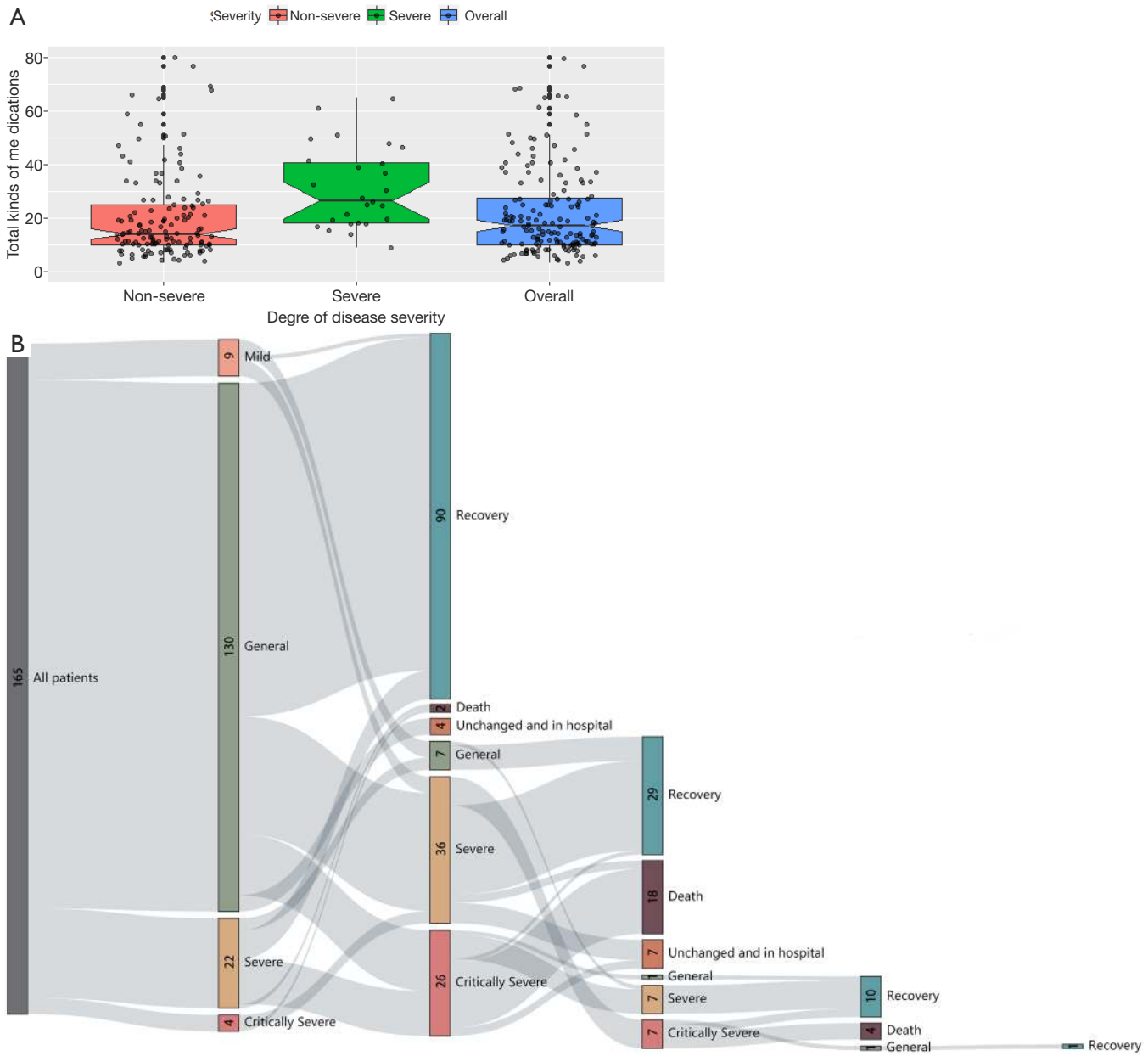

Figure 1 The total kinds of medications and disease progression for 165 patients with coronavirus disease 2019 (COVID-19). (A) The total kinds of medications grouped by disease severity and comorbidities. Total kinds of medications refer to the medications (generic names) per person used during the whole hospitalization. Antivirals were defined as Anatomical Therapeutic Chemical (ATC) classification codes starting with J05. (B) The disease progression for 165 patients since baseline. The patient's baseline condition was classified into 4 levels according to the guidelines "*Diagnostic and treatment protocol for Novel Coronavirus Pneumonia (trial version 5)*": mild, general, severe, and critically severe, respectively.

or transferred to other hospitals. *Figure 1B* shows the cumulative outcomes of the patient cohort. It can be seen that 11.1% (1/9), 12.3% (16/130), 36.4% (8/22), and 25.0% (1/4) of the patients progressed to a worse condition or even death for those with baseline mild, general, severe, and critically severe levels, respectively. Compared with the non-severe subgroup, the patients in the severe subgroup experienced a significantly higher percentage of death

Table 3 Outcomes of death or disease exacerbation after admission for patients using different drugs

Drug categories	Disease exacerbation after admission (n=65)			Death during hospital days (n=24)		
	Never used (n, %)	Ever used (n, %)	P value	Never used (n, %)	Ever used (n, %)	P value
Antivirals	2/12 (16.7)	63/153 (41.2)	0.1279	1/12 (8.3)	23/153 (15.0)	>0.9999
α-interferon	42/94 (44.7)	23/71 (32.4)	0.1098	16/94 (17.0)	8/71 (11.3)	0.2993
Lopinavir/ritonavir	56/142 (39.4)	9/23 (39.1)	0.9778	19/142 (13.4)	5/23 (21.7)	0.3367
Ribavirin	63/162 (38.9)	2/3 (66.7)	0.5623	23/162 (14.2)	1/3 (33.3)	0.3779
Arbidol	61/151 (40.4)	4/14 (28.6)	0.3863	22/151 (14.6)	2/14 (14.3)	>0.9999
Oseltamivir	7/40 (17.5)	58/125 (46.4)	0.0011	1/40 (2.5)	23/125 (18.4)	0.0130
Others	62/158 (39.2)	3/7 (42.9)	>0.9999	24/158 (15.2)	0/7 (0.0)	0.5950
Antibacterials	1/2 (50.0)	64/163 (39.3)	>0.9999	1/2 (50.0)	23/163 (14.1)	0.2705
Moxifloxacin	6/12 (50.0)	59/153 (38.6)	0.5425	3/12 (25.0)	21/153 (13.7)	0.3854
Ceftriaxone-tazobactam	37/102 (36.3)	28/63 (44.4)	0.2967	16/102 (15.7)	8/63 (12.7)	0.5969
Cefoperazone-tazobactam	54/131 (41.2)	11/34 (32.4)	0.3457	21/131 (16.0)	3/34 (8.8)	0.4148
Cefoperazone-sulbactam	49/132 (37.1)	16/33 (48.5)	0.2321	16/132 (12.1)	8/33 (24.2)	0.0971
Levofloxacin	50/132 (37.9)	15/33 (45.5)	0.4257	23/132 (17.4)	1/33 (3.0)	0.0496
Meropenem	46/134 (34.3)	19/31 (61.3)	0.0056	21/134 (15.7)	3/31 (9.7)	0.5733
Amoxicillin-flucloxacillin	48/137 (35.0)	17/28 (60.7)	0.0113	17/137 (12.4)	7/28 (25.0)	0.1358
Biapenem	48/145 (33.1)	17/20 (85.0)	<0.0001	14/145 (9.7)	10/20 (50.0)	<0.0001
Piperacillin-tazobactam	52/145 (35.9)	13/20 (65.0)	0.0124	15/145 (10.3)	9/20 (45.0)	0.0004
Imipenem-cilastatin	52/147 (35.4)	13/18 (72.2)	0.0025	14/147 (9.5)	10/18 (55.6)	<0.0001
Cefminox	57/150 (38.0)	8/15 (53.3)	0.2465	22/150 (14.7)	2/15 (13.3)	>0.9999
Linezolid	55/152 (36.2)	10/13 (76.9)	0.0039	17/152 (11.2)	7/13 (53.8)	0.0006
All other antibacterials	41/119 (34.5)	24/46 (52.2)	0.0367	11/119 (9.2)	13/46 (28.3)	0.0019
Glucocorticoids	13/50 (26.0)	52/115 (45.2)	0.0202	2/50 (4.0)	22/115 (19.1)	0.0113
Antimycotics	47/135 (34.8)	18/30 (60.0)	0.0107	15/135 (11.1)	9/30 (30.0)	0.018
General nutrients	4/38 (10.5)	61/127 (48.0)	<0.0001	2/38 (5.3)	22/127 (17.3)	0.0643
Traditional Chinese medicine	28/64 (43.8)	37/101 (36.6)	0.362	10/64 (15.6)	14/101 (13.9)	0.7542
Vasoactive drugs	38/125 (30.4)	27/40 (67.5)	<0.0001	4/125 (3.2)	20/40 (50.0)	<0.0001
Intestinal microecological regulators	53/133 (39.8)	12/32 (37.5)	0.8071	17/133 (12.8)	7/32 (21.9)	0.2609
Immunoglobulins	55/137 (40.1)	10/28 (35.7)	0.6619	23/137 (16.8)	1/28 (3.6)	0.0816

Data are presented as no. (%).

(34.6% *vs.* 7.2%, P=0.001) and a shorter period from hospital admission to ICU admission (median, 3 *vs.* 6 days; IQR, 0–5 *vs.* 4–8 days, P<0.001). For the 24 death cases, a total of 16 patients (66.7%) deteriorated (7, 29.2%) or even died (9, 70.8%) within the first 7 days of hospitalization (Figure S2). There were no differences observed in the rate of disease exacerbation or death during hospitalization between patients who ever used antivirals, antibacterials, TCM, intestinal microecological regulators, and immunoglobulins (*Table 3*). In the patients who had disease exacerbation or died during hospitalization, 'antivirals + glucocorticoids + TCM' was the most common medication

Table 4 Outcomes of death or disease exacerbation after admission for patients using different drug combinations

Medication combinations	Disease progression				Disease mortality			
	Overall	Non-exacerbation	Exacerbation	P value	Overall	Non-death	Death	P value
Antivirals + glucocorticoids + TCM	81 (49.1)	42 (51.9)	39 (48.1)	0.0169	81 (49.1)	61 (75.3)	20 (24.7)	<0.0001
Antivirals + glucocorticoids	23 (13.9)	12 (52.2)	11 (47.8)		23 (13.9)	22 (95.7)	1 (4.3)	
Antivirals + TCM	22 (13.3)	19 (86.4)	3 (13.6)		22 (13.3)	22 (100.0)	0 (0.0)	
Only antivirals	27 (16.4)	17 (63.0)	10 (37.0)		27 (16.4)	25 (92.6)	2 (7.4)	
Others (all without antivirals)	12 (7.3)	10 (83.3)	2 (16.7)		12 (7.3)	11 (91.7)	1 (8.3)	

Data are presented as n (%). TCM, traditional Chinese medicine.

combination (*Table 4*).

Safety assessment

Two senior clinical pharmacists independently evaluated the association between AEs in patients and their medication regimens. The basic criteria for distinguishing AEs with COVID-19 related presentation included excluding any patient who had liver or kidney injury history and presented with abnormal liver or kidney function on admission. There were 53 (32.1%) cases of AEs, of which 13 patients (7.9%) had elevated liver enzymes, 49 patients (29.7%) presented with worsening kidney function, and 9 patients had both. A total of 157 tested patients without liver injury history presented an average AST level of 34.0 (22.0–61.0) U/L in blood. The number of cases with elevated blood AST enzymes was 7.9% (11/139) and 15.4% (4/26) in severe and non-severe patients, respectively, and the difference in the average level between the 2 groups was statistically significant (P=0.002). A total of 159 patients were subjected to ALT tests, and the average level was 30.0 (17.0–68.0) U/L. As for patients with abnormal blood ALT levels, the number of cases was also 7.9% (11/139) and 15.4% (4/26) for the 2 groups, respectively, and the difference in average level between the 2 groups was also statistically significant (P=0.003). Also, 45 (31.5%), 25 (42.4%), and 30 (66.7%) patients presented with worsening kidney function as determined by the 3 indicators of creatinine, EGFR, and urine protein, respectively, among 143, 59, and 45 patients tested without chronic kidney disease (CKD) history (*Table 5*).

Discussion

To our knowledge, this is one of the earliest studies to describe the detailed patterns of medication, disease progression, as well as safety issues for hospitalized patients with COVID-19. We also found that the prescriptions were diverse in practice, and most of the medications were prescribed considering the patient's characteristics, including disease severity, age, comorbidities, and AEs. However, the almost universal use of antibacterials might have caused a significant proportion of liver injury or kidney injury. Our findings provide important clues for further explorations, especially regarding treatment timing and safety issues.

The clinical features of patients with COVID-19 in our study were consistent with 4 recent reports, with fever as the predominant symptom (6-9). Compared with the non-severe patients, the severe subgroup cases were significantly older and were more likely to have comorbidities, and these findings were also compatible with 2 previous studies (6,9). Nearly all patients in this study received antibacterials, 92.7% received antivirals, and 69.7% received glucocorticoids. These results were following 3 recent investigations conducted in Wuhan (7-9), but were significantly higher than the 2 latest reports outside Wuhan (5,6). This inconsistency might be because patients outside Wuhan in the previous studies were at least 8 years younger, with less severe disease and comorbidities (5,6,8,9). An unsurprising finding of our study is that clinicians tried several drugs and even more drug combinations as potential pharmaceutical options against COVID-19, even within a single hospital. The diverse medication regimens might be because no specific treatment has been recommended for COVID-19 until now, and the evolution and revisions to the government guidelines (trial) for the diagnosis and treatment of COVID-19 are constant (10-13,27). Over 200 studies have already been registered on either ClinicalTrials.gov or Chictr.org, to test medications that fight other viruses (e.g., flu and HIV), TCM, stem cells, steroids, and plasma treatment. However, we have to accept that all treatment explorations require processes of a certain

Table 5 Test results and liver and kidney adverse events of COVID-19 patients

Test results	Non-severe group (n=139)				Severe group (n=26)			
	All patients	Abnormal	Normal	P value	All patients	Abnormal	Normal	P value
AST (U/L)								
Sample size	134	11	123		23	4	19	
Median (IQR)	31.5 (22.0–54.0)	134.0 (48.0–180.0)	30.0 (21.0–45.0)	<0.0001	68.0 (48.0–81.0)	187.0 (167.5–204.0)	63.0 (36.0–71.0)	0.002
ALT (U/L)								
Sample size	134	11	123		25	4	21	
Median (IQR)	26.0 (16.0–58.0)	184.0 (88.0–279.0)	24.0 (15.0–47.0)	<0.0001	59.0 (30.0–91.0)	172.0 (133.5–254.0)	55.0 (27.0–79.0)	0.003
CRE								
Sample size	121	31	90		22	14	8	
Median (IQR)	68.7 (57.3–82.0)	88.4 (65.7–106.4)	65.5 (55.8–78.7)	<0.0001	75.6 (60.4–110.8)	85.0 (65.4–118.0)	66.2 (54.6–73.4)	0.027
EGFR								
Sample size	50	20	30		9	5	4	
Median (IQR)	107.0 (83.1–119.7)	78.5 (69.6–89.5)	114.1 (105.4–122.0)	<0.0001	111.6 (80.4–115.7)	80.4 (71.4–120.6)	112.0 (110.7–114.0)	0.713
Upro								
Sample size	33	21	12		12	9	3	
–	13	1 (7.7)	12 (92.3)	<0.0001	3	0 (0.0)	3 (100.0)	0.005
±	9	9 (100.0)	0 (0.0)		2	2 (100.0)	0 (0.0)	
+	6	6 (100.0)	0 (0.0)		2	2 (100.0)	0 (0.0)	
++	4	4 (100.0)	0 (0.0)		5	5 (100.0)	0 (0.0)	
+++	1	1 (100.0)	0 (0.0)		0	0	0	

Data are presented as no. (%) or median (IQR). AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRE, creatinine; EGFR, estimated glomerular filtration rate; Upro, urine protein; IQR, interquartile range.

time frame (28) and that the current state of chaos will inevitably last for some time. Therefore, to sum up, it is critical to further investigate drug utilization and potential experiences promptly like our study in order to provide real-world evidence for clinical decision-makers.

A higher proportion and a longer duration of glucocorticoids are worth noting in this study. Current WHO guidance and several researchers have recommended that corticosteroids should not be used due to COVID-19-induced lung injury or shock (17,23). In contrast, an expert consensus statement developed by the Chinese Thoracic Society on February 11 points out that corticosteroids should not be abandoned in treating COVID-19 due to inconclusive clinical evidence (19). According to this statement, the dose should be low-to-moderate (≤0.5–1 mg/kg per day methylprednisolone or equivalent), and the duration should be short (≤7 days). Our study indicated that almost all the single doses of corticosteroids were already consistent with this statement. This might due to this hospital having developed rapid guidelines before January 29 (27), with a weak recommendation that 40 to 80 mg of methylprednisolone per day could be considered. However, approximately half of the patients were treated with corticosteroids for more than 7 days, which was more serious in severe patients. This finding was consistent with 2 previous studies completed before developing the expert

consensus statement (8). The main reason is most likely due to the rapid development of this hospital's guidelines, which did not mention the duration. The current national guidelines recommend that glucocorticoids should be restricted within 3–5 days (6,10-13) if needed. Considering corticosteroid treatment is a 'double-edged sword' (19), our finding is worthy of front-line physicians' and researchers' attention.

Another phenomenon that should be noted is the almost universal empirical antibacterial treatment. This result was in agreement with 3 studies conducted in Wuhan (6,7,9) but was twice the level of the latest study outside Wuhan (5). The difference in the distribution of age and comorbidities between Xu *et al.*'s study and ours might partially explain this gap in the antibacterial usage rate (5). Also, inadequate supplies of specific detection kits in Wuhan during late January and early February 2020 brought about difficulties in making rapid etiology diagnoses of COVID-19 in patients on admission, resulting in requests for empirical antibacterial treatment to rule out a bacterial infection, and consequently increased antibacterial usage rates. All COVID-19 treatment statements in China emphasized to avoid inappropriate use of antibacterials, especially the combination of broad-spectrum antibacterials (10-13,27). In this study, we observed possible AEs in the liver and kidney at a common level (over 5%).

Interestingly, these safety signals have also been reported by some antibacterial instructions and previous studies (29-31). The kidneys' potential harm was also well summarized in previous studies for amoxicillin (30) and cloxacillin sodium (31). The widespread use of antibacterials, together with multiple drugs, should alert clinicians to pay attention to the potential ADEs (32).

Our study focused on drug utilization and disease progression from real-world data. Some limitations should be noted in this study. First, only 165 patients from a single hospital were included, and 3.0% of patients were still hospitalized at the time of database locking. However, despite this, the results of this study permitted an early assessment. Second, with the limited number of non-severe cases, only age, sex, and the number of comorbidities were taken into consideration, and additional confounders might still have existed. Although almost all antivirals and antibacterials (the most common treatments in our study) were not over-the-counter medications in China (33), it is unknown what percentage of patients obtained the drugs from outpatient services. Therefore, the percentage of pre-hospitalization medications should be further considered in future investigations.

Conclusions

In summary, the drug utilization for hospitalized patients with COVID-19 was diverse and generally complied with China's existing guidelines. Also, AEs should not be ignored in the process of drug prescriptions. Given our preliminary investigation, there is a need for multicenter research with larger sample size and longer follow-up period in the future in order to promote a more solid basis for medication recommendations.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The corresponding author had access to all data in the study and had final responsibility for the decision to submit for publication. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Ethics Board of Zhongnan Hospital of Wuhan University (No. 2020014). Written informed consent was waived for emerging infectious diseases.

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Supplementary

Table S1 Comparison of the latest four versions of "Diagnosis and treatment protocol for Novel Coronavirus Pneumonia (trial version)"

Date issued	Subtype	Version 3rd	Version 4th	Version 5th	Version 6th	Version 7th
		Jan, 22	Jan, 27	Feb, 04	Feb, 18	Mar, 03
Severe group and critical severe group	Oxygen therapy	Not mentioned.	Not mentioned.	Nasal cannula, mask oxygen.	Same as the 5th version.	Same as the 5th version.
	Mechanical ventilation/ respiratory support	NIV; invasive mechanical ventilation (take lung protective ventilation strategies, if necessary, use supine ventilation or lung recruitment); ECMO therapy.		Add: HFNO therapy. Add: salvage therapy: lung recruitment or ECMO.	Same as the 5th version.	Add: closed sputum aspiration or bronchoscopy examination if conditions need
	Circulation support	On the basis of full fluid resuscitation, improve microcirculation, use vasoactive drugs; if necessary, use hemodynamic monitoring.				Add: closely monitor blood pressure, heart rate and urine. Add: pay attention to liquid balance strategy to avoid excessive and insufficient.
	Glucocorticoids therapy	Not mentioned.	(1) Systemic use of glucocorticoids needs to be cautious, according to the severity of the disease, methylprednisolone per day can be considered in a short time (3~5 days), the total daily dose should not exceed 1~2 mg/kg. (2) Xuebijing injection 50ml iv bid. (3) Use intestinal microecological regulators. (4) Convalescent plasma therapy may be considered if conditions permit.	Add: pay attention to the immunosuppressive effect, which can delay the recognition of coronavirus.	Add: glucocorticoids could be used as appropriate for patients with rapid imaging progress and overreacts with inflammation.	Same as the 6th version.
	Plasma therapy (convalescent patients Plasma)	Not mentioned.	It could be considered if conditions permit.	Add: extracorporeal blood purification techniques may be considered if high inflammatory response occurs.	Recommend.	Recommend.
	Renal failure and renal replacement therapy	Not mentioned.	Not mentioned.	Not mentioned.	Not mentioned.	Pay attention to liquid balance, acid base balance and electrolyte balance. In terms of nutritional support, pay attention to nitrogen balance, calories and trace element supplements. CRRT may be used in severe cases.
	Blood purification therapy	Not mentioned.	Not mentioned.	Not mentioned.	Not mentioned.	Plasma exchange, adsorption, perfusion, blood/plasma filtration, etc., used in the early and middle treatment of severe and critical patients with cytokine storm.
	Immunotherapy	Not mentioned.	Not mentioned.	Not mentioned.	Not mentioned.	In patients with extensive lung lesions and severe lung disease, laboratory detection of elevated il-6 levels: tocilizumab, initial dose 4-8mg/kg, the recommended dose is 400mg, diluted to 100ml with 0.9% normal saline, and infusion time is greater than 1 hour. For patients with poor efficacy of the first dose, 1 additional dose can be applied after 12 hours (the dose is the same as before), with the maximum of 2 cumulative doses and the maximum single dose not exceeding 800mg. Pay attention to the allergic reactions, patients with tuberculosis and other active infection is contraindicated.
	Others	Not mentioned.	Strengthen psychological counseling.	Same as the 4th version.	Same as the 4th version.	Add: children with severe or critical cases, Intravenous infusion of gamma globulin may be considered. Add: pregnant women with severe or critical cases should actively terminate their pregnancy, preferred Cesarean.
General treatment						
	Supportive treatment	(1) Sufficient energy and nutrients. (2) Bed rest. (3) Balance for water, electrolytes, acid base levels and other internal environment factors.				
	Close monitoring	Vital signs (blood routine, urine routine, CRP, organ function (liver enzyme, myocardial enzyme, creatinine, urea nitrogen, urine volume, etc), coagulation function, arterial blood gas analysis and chest imaging, etc).		Add: test cytokine if conditions permit.	Same as the 5th version.	Same as the 5th version.
	Oxygen therapy	(1) Nasal cannula, oxygen. (2) If necessary, use HFNO therapy, NIV or invasive mechanical ventilation.		No longer recommended NIV or invasive mechanical ventilation as general treatment, only for severe and critical severe group patients.	Same as the 5th version.	Same as the 5th version.
	Antiviral therapy	(1) The α-interferon atomization inhalation 5 million U per time in sterile injection water, bid (for adults). (2) Lopinavir/litonavir orally, 2 capsules each time, bid.	Add: Lopinavir/litonavir (200mg/50mg) orally, 2 capsules each time, bid.	Add: recommend Ribavirin 500mg iv bid/tid in combination (for adults)[a], Pay attention to the adverse reactions of Lopinavir/litonavir and drug interactions.	Add: recommend Ribavirin 500mg iv bid/tid in combination, with α-interferon or Lopinavir/litonavir (for adults); Pay attention to the adverse reactions of Lopinavir/litonavir and drug interactions. Add: Chloroquine Phosphate 500mg bid (for adults); Arbidol 200mg tid (for adults, less than 10days); Not recommended using more than 3 kinds of antiviral drugs at the same time, when intolerable side effects occurs, stop using related drugs.	Add: Chloroquine Phosphate : 500mg bid 7days (for 18-65 years adult, weight > 50kg); 500mg bid for the first two days, 500mg qd for the third to seventh days (for for 18-65 years adult, weight <50kg). Add: pay attention to the drug contraindications, chloroquine is contraindicated in patients with cardiac adverse reactions. Add: for pregnant women, consider the number of weeks of gestation, choose drugs with less impact on the fetus as far as possible, and whether to terminate the pregnancy and other issues.
	Antibacterial therapy	Avoid blind or inappropriate use of antibacterials, especially the combination of broad-spectrum antibacterials, enhancement of bacteriological surveillance should be performed and promptly given appropriate drugs when it occurs secondary bacterial infection.				
	Glucocorticoids therapy	Systemic use of glucocorticoids needs to be cautious, according to the severity of the disease, methylprednisolone per day can be considered in a short time (3~5 days), the total daily dose should not exceed 1~2 mg/kg.	No longer recommended glucocorticoids as general treatment, but only limited as the choice for severe and critical severe group.			
	Traditional Chinese medicine	Treat the patient based on syndromes differentiation individually, different versions of the guidelines have been further refined the corresponding recommendations in detail.				

[a], February 04, 2020-February 08, 2020, ribavirin was recommended: ribavirin 1.2g iv q8h with the first dose was 4g or ribavirin 8mg/kg iv q8h (for adults). ECMO, extracorporeal membrane oxygenation; HFNO, high-flow nasal oxygen therapy; NIV, non-invasive ventilation; CRRT, continuous renal replacement therapy.

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Table S2 Clinical features of 165 patients with coronavirus disease 2019 (COVID-19)

Clinical features	All patients (n=165)	Baseline disease severity[a]		P value
		Non-severe group (n=139)	Severe group (n=26)	
Symptoms and signs				
Fever	125 (75.8)	102 (73.4)	23 (88.5)	0.100
Fatigue	20 (12.1)	18 (12.9)	2 (7.7)	0.743
Dry cough	4 (2.4)	4 (2.9)	0 (0.0)	1.000
Anorexia	3 (1.8)	2 (1.4)	1 (3.8)	0.404
Myalgia	7 (4.2)	7 (5.0)	0 (0.0)	0.598
Dyspnea or shortness of breath	12 (7.3)	6 (4.3)	6 (23.1)	0.004
Chill	2 (1.2)	2 (1.4)	0 (0.0)	1.000
Expectoration	13 (7.9)	11 (7.9)	2 (7.7)	1.000
Pharyngalgia	5 (3.0)	3 (2.2)	2 (7.7)	0.177
Diarrhea or abdominal pain	9 (5.5)	8 (5.8)	1 (3.8)	>0.9999
Nausea or vomiting	5 (3.0)	4 (2.9)	1 (3.8)	0.581
Dizziness or headache	4 (2.4)	4 (2.9)	0 (0.0)	>0.9999
Nasal congestion	2 (1.2)	1 (0.7)	1 (3.8)	0.291
Enlargement of lymph nodes	1 (0.6)	1 (0.7)	0 (0.0)	>0.9999
No. of Symptoms and signs	1 (1-2)	1 (1-2)	1 (1-2)	0.300
Days of fever	10 (5-14)	9 (5-13)	15 (10-24)	0.007
Abnormalities on chest CT				
Ground-glass opacity	4 (2.4)	4 (2.9)	0 (0.0)	>0.9999
Bilateral patchy shadowing	3 (1.8)	3 (2.2)	0 (0.0)	>0.9999

[a], the patient's baseline condition was classified into four levels according to the guidelines: mild, general, severe, critical severe, respectively, the first two levels were further classified as a non-severe subgroup and the latter two as a severe subgroup. Data are presented as No. (%) or median (IQR).

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Table S3 The combination and the number of the medications for 165 patients with coronavirus disease 2019 (COVID-19)

	Administering Medication			P value
	All patients (n=165)	Disease severity[a]		
		Non-Severe Group (n=139)	Severe group (n=26)	
Antivirals[b]	153 (92.7)	129 (92.8)	24 (92.3)	>0.9999
Medication combination[c]				0.209
Antivirals + glucocorticoids + TCM	81 (49.1)	66 (47.5)	15 (57.7)	
Antivirals + glucocorticoids	23 (13.9)	17 (12.2)	6 (23.1)	
Only antivirals	27 (16.4)	25 (18.0)	2 (7.7)	
Antivirals + TCM	22 (13.3)	21 (15.1)	1 (3.8)	
Others (all without antivirals)	12 (7.3)	10 (7.2)	2 (7.7)	
Total kinds of all medications (generic names)				
Overall	17 (10-29)	15 (10-27)	27 (18-41)	<0.0001
With comorbidities	21 (14.5-39.5)	20 (13-37)	28 (19-46)	0.103
Without comorbidities	12 (8-19)	11 (8-19)	22.5 (17.5-33)	0.034
Total kinds of all antiviral medications (generic names)	1 (1-2)	1 (1-2)	1 (1-2)	0.206

Data are presented as No. (%) or median (IQR). [a], the patient's baseline condition was classified into four levels according to the guidelines: mild, general, severe, critical severe, respectively, the first two levels were further classified as a non-severe subgroup and the latter two as a severe subgroup. [b], antivirals was defined as Anatomical Therapeutic Chemical (ATC) classification codes started with J05, glucocorticoids (H02AB), traditional Chinese medicine (TCM, identified using drug name). [c], medication combination analysis were concentrated on antivirals, glucocorticoids and TCM (traditional Chinese medicine) without considering other coexisting medications. IQR, interquartile range.

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Table S4 Dose distribution of antivirals and glucocorticoids for patients with coronavirus disease 2019 (COVID-19)

	All patients (n=165)	Baseline disease severity[a]		P value
		Non-severe group (n=139)	Severe group (n=26)	
Antivirals[b]				
α-interferon				
No. of its prescription	107 (100.0)	92 (86.0)	15 (14.0)	0.002
3 million U	79 (73.8)	73 (79.3)	6 (40.0)	
5 million U	24 (22.4)	15 (16.3)	9 (60.0)	
Others (power, etc.)	4 (3.7)	4 (4.3)	0 (0.0)	
Lopinavir/litonavir				
No. of its prescription	35 (100.0)	27 (77.1)	8 (22.9)	0.237
2·00 co	27 (77.1)	20 (74.1)	7 (87.5)	
400·00 co	6 (17.1)	6 (22.2)	0 (0.0)	
Others (tablet, etc.)	2 (5.7)	1 (3.7)	1 (12.5)	
Arbidol				
No. of its prescription	20 (100.0)	20 (100.0)	0 (0.0)	-
200·00 mg	19 (95.0)	19 (95.0)	0 (0.0)	
Others (dispersible tablet, etc.)	1 (5.0)	1 (5.0)	0 (0.0)	
Oseltamivir				
No. of its prescription	419 (100.0)	361 (86.2)	58 (13.8)	0.835
150.00 mg	16 (3.8)	13 (3.6)	3 (5.2)	
75.00 mg	324 (77.3)	279 (77.3)	45 (77.6)	
Capsule	77 (18.4)	67 (18.6)	10 (17.2)	
Others (Granules)	2 (0.5)	2 (0.6)	0 (0.0)	
Glucocorticoids[c]				
Hexadecadrol				
No. of its prescription	75 (100.0)	72 (96.0)	3 (4.0)	>0.9999
3.00 mg	68 (90.7)	65 (90.3)	3 (100.0)	
5.00 mg	4 (5.3)	4 (5.6)	0 (0.0)	
Others (7.50 mg, 20.00 mg, or hydro-acupuncture)	3 (4.0)	3 (4.2)	0 (0.0)	
Methylprednisolon				
No. of its prescription	373 (100.0)	293 (78.6)	80 (21.4)	0.039
20.00 mg	198 (53.1)	158 (53.9)	40 (50.0)	
40.00 mg	83 (22.3)	67 (22.9)	16 (20.0)	
60.00 mg	33 (8.8)	23 (7.8)	10 (12.5)	
80.00 mg	30 (8.0)	18 (6.1)	12 (15.0)	
Others (power, etc.)	16 (4.3)	15 (5.1)	1 (1.3)	
Other dosage	13 (3.5)	12 (4.1)	1 (1.3)	

Data are presented as No. (%) or median (IQR). [a], the patient's baseline condition was classified into four levels according to the guidelines: mild, general, severe, critical severe, respectively, the first two levels were further classified as a non-severe subgroup and the latter two as a severe subgroup. [b], antivirals was defined as Anatomical Therapeutic Chemical (ATC) classification codes started with J05. [c], glucocorticoids was defined as Anatomical Therapeutic Chemical (ATC) classification codes started with H02AB. NA, not applicable; IQR, interquartile range.

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Table S5 Baseline features of all patients with coronavirus disease 2019 (COVID-19) who started treatment with or without antivirals

Features	Antivirals[a]		P value
	Without (n=12)	With (n=153)	
Age (y)			
Median (IQR)	53 (37-64)	56 (42-67)	0.565
Groups			
15-49	5 (41.7)	54 (35.3)	0.931
50-64	4 (33.3)	51 (33.3)	
≥65	3 (25.0)	48 (31.4)	
Sex female	7 (58.3)	74 (48.4)	0.506
Comorbidities			
Any	4 (33.3)	80 (52.3)	0.206
No. of comorbidities	0 (0-2)	1 (0-2)	0.230
Disease severity[b]			>0.9999
Non-severe group	10 (83.3)	129 (84.3)	
Severe group	2 (16.7)	24 (15.7)	
Outcomes			
Days of imaging tests changing to negative (-)	9 (9-9)	9 (6-13)	0.608
Days of nucleic acid tests changing to negative (-)	9 (9-9)	6 (4-8)	0.256
Death	1 (8.3)	23 (15.0)	0.870
Recovered	10 (83.3)	120 (78.4)	
Staying in hospital/transferred to another hospital	1 (8.3)	10 (6.5)	

Data are presented as No. (%) or median (IQR). [a], antivirals was defined as Anatomical Therapeutic Chemical (ATC) classification codes started with J05. [b], The patient's baseline condition was classified into four levels according to the guidelines: mild, general, severe, critical severe, respectively, the first two levels were further classified as a non-severe subgroup and the latter two as a severe subgroup. IQR, interquartile range.

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Table S6 Baseline features of all patients with coronavirus disease 2019 (COVID-19) who started treatment with or without glucocorticoids

Features	Glucocorticoids[a]		P value
	Without (n=52)	With (n=113)	
Age (y)			
Median (IQR)	54 (37-61)	58 (42-70)	0.194
Groups			
15-49	19 (38.0)	40 (34.8)	0.107
50-64	21 (42.0)	34 (29.6)	
≥65	10 (20.0)	41 (35.7)	
Sex female	31 (62.0)	50 (43.5)	0.029
Comorbidities			
Any	25 (50.0)	59 (51.3)	0.878
No. of comorbidities	1 (0-2)	1 (0-2)	0.896
Disease severity[b]			
Non-Severe group	47 (94.0)	92 (80.0)	0.023
Severe group	3 (6.0)	23 (20.0)	
Outcomes			
Days of imaging tests changing to negative (-)	8 (4-11)	10 (8-14)	0.058
Days of nucleic acid tests changing to negative (-)	5 (2-5)	7 (5-9)	0.042
Death	2 (4.0)	22 (19.1)	0.020
Recovered	46 (92.0)	84 (73.0)	
Staying in hospital/ transferred to another hospital	2 (4.0)	9 (7.8)	

Data are presented as No. (%) or median (IQR). [a], glucocorticoids was defined as Anatomical Therapeutic Chemical (ATC) classification codes started with H02AB. [b], the patient's baseline condition was classified into four levels according to the guidelines: mild, general, severe, critical severe, respectively, the first two levels were further classified as a non-severe subgroup and the latter two as a severe subgroup. IQR, interquartile range.

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Table S7 Baseline features of all patients with coronavirus disease 2019 (COVID-19) who started treatment with or without antimycotics

Features	Antimycotics[a]		P value
	Without (n=141)	With (n=24)	
Age (y)			
Median (IQR)	54 (39-65)	67 (50-80)	0.004
Groups			
15-49	52 (38.5)	7 (23.3)	0.003
50-64	49 (36.3)	6 (20.0)	
≥65	34 (25.2)	17 (56.7)	
Sex female	66 (48.9)	15 (50.0)	0.912
Comorbidities			
Any	65 (48.1)	19 (63.3)	0.132
No. of comorbidities	0 (0-2)	2 (0-3)	0.107
Disease severity[b]			
Non-severe group	113 (83.7)	26 (86.7)	0.789
Severe group	22 (16.3)	4 (13.3)	
Outcomes			
Days of imaging tests changing to negative (-)	9 (6-12)	14 (7-20)	0.974
Days of nucleic acid tests changing to negative (-)	6 (4-8)	5 (2-11)	0.562
Death	15 (11.1)	9 (30.0)	<0.0001
Recovered	116 (85.9)	14 (46.7)	
Staying in hospital/transferred to another hospital	4 (3.0)	7 (23.3)	

Data are presented as No. (%) or median (IQR). [a], antimycotics was defined as Anatomical Therapeutic Chemical (ATC) classification codes started with J02. [b], the patient's baseline condition was classified into four levels according to the guidelines: mild, general, severe, critical severe, respectively, the first two levels were further classified as a non-severe subgroup and the latter two as a severe subgroup. IQR, interquartile range.

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Table S8 Baseline features of all patients with coronavirus disease 2019 (COVID-19) who started treatment with or without general nutrients

Features	General nutrients[a]		P value
	Without (n=39)	With (n=126)	
Age (y)			
Median (IQR)	51 (34-65)	57 (43-67)	0.487
Groups			
15-49	18 (47.4)	41 (32.3)	0.231
50-64	10 (26.3)	45 (35.4)	
≥65	10 (26.3)	41 (32.3)	
Sex female	24 (63.2)	57 (44.9)	0.048
Comorbidities			
Any	12 (31.6)	72 (56.7)	0.007
No. of comorbidities	0 (0-1)	1 (0-2)	0.007
Disease severity[b]			
Non-severe group	35 (92.1)	104 (81.9)	0.129
Severe group	3 (7.9)	23 (18.1)	
Outcomes			
Days of imaging tests changing to negative (-)	9 (8-12)	9 (6-13)	0.914
Days of nucleic acid tests changing to negative (-)	6 (4-7)	6 (4-9)	0.894
Death	2 (5.3)	22 (17.3)	0.073
Recovered	35 (92.1)	95 (74.8)	
Staying in hospital/transferred to another hospital	1 (2.6)	10 (7.9)	

Data are presented as No. (%) or median (IQR). [a], general nutrients was defined as Anatomical Therapeutic Chemical (ATC) classification codes started with V06. [b], the patient's baseline condition was classified into four levels according to the guidelines: mild, general, severe, critical severe, respectively, the first two levels were further classified as a non-severe subgroup and the latter two as a severe subgroup. IQR, interquartile range.

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Table S9 Baseline features of all patients with coronavirus disease 2019 (COVID-19) who started treatment with or without traditional Chinese medicine

Features	Traditional Chinese medicine[a]		P value
	Without (n=74)	With (n=91)	
Age (y)			
Median (IQR)	57 (44-67)	55 (37-66)	0.485
Groups			
15-49	25 (39.1)	34 (33.7)	0.524
50-64	18 (28.1)	37 (36.6)	
≥65	21 (32.8)	30 (29.7)	
Sex Female	30 (46.9)	51 (50.5)	0.650
Comorbidities			
Any	37 (57.8)	47 (46.5)	0.158
No. of comorbidities	1 (0-2)	0 (0-2)	0.149
Disease severity[b]			
Non-severe group	51 (79.7)	88 (87.1)	0.201
Severe group	13 (20.3)	13 (12.9)	
Outcomes			
Days of imaging tests changing to negative (-)	9 (6-12)	10 (6-14)	0.163
Days of nucleic acid tests changing to negative (-)	5 (3-7)	7 (4-10)	0.270
Death	10 (15.6)	14 (13.9)	0.702
Recovered	51 (79.7)	79 (78.2)	
Staying in hospital/transferred to another hospital	3 (4.7)	8 (7.9)	

Data are presented as No. (%) or median (IQR). [a], traditional Chinese medicine was defined as Anatomical Therapeutic Chemical (ATC) classification codes started with TCM, identified using drug name. [b], the patient's baseline condition was classified into four levels according to the guidelines: mild, general, severe, critical severe, respectively, the first two levels were further classified as a non-severe subgroup and the latter two as a severe subgroup. IQR, interquartile range.

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Table S10 Baseline features of all patients with coronavirus disease 2019 (COVID-19) who started treatment with or without vasoactive drugs

Features	Vasoactive drugs[a]		P value
	Without (n=128)	With (n=37)	
Age (y)			
Median (IQR)	52 (37-64)	66 (54-78)	0.003
Groups			
15-49	53 (42.4)	6 (15.0)	0.001
50-64	42 (33.6)	13 (32.5)	
≥65	30 (24.0)	21 (52.5)	
Sex female	66 (52.8)	15 (37.5)	0.092
Comorbidities			
Any	55 (44.0)	29 (72.5)	0.002
No. of comorbidities	0 (0-1)	2 (0-3)	0.001
Disease severity[b]			
Non-severe group	112 (89.6)	27 (67.5)	0.001
Severe group	13 (10.4)	13 (32.5)	
Outcomes			
Days of imaging tests changing to negative (-)	9 (6-12)	13 (9-16)	0.451
Days of nucleic acid tests changing to negative (-)	6 (5-9)	5 (3-6)	0.283
Death	4 (3.2)	20 (50.0)	0.000
Recovered	116 (92.8)	14 (35.0)	
Staying in hospital/transferred to another hospital	5 (4.0)	6 (15.0)	

Data are presented as No. (%) or median (IQR). [a], vasoactive drugs was defined as Anatomical Therapeutic Chemical (ATC) classification codes started with C01DA, C01CA, C04AB01. [b], the patient's baseline condition was classified into four levels according to the guidelines: mild, general, severe, critical severe, respectively, the first two levels were further classified as a non-severe subgroup and the latter two as a severe subgroup. IQR, interquartile range.

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Table S11 Baseline features of all patients with coronavirus disease 2019 (COVID-19) who started treatment with or without intestinal microecological regulators

Features	Intestinal microecological regulators[a]		P value
	Without (n=138)	With (n=27)	
Age (y)			
Median (IQR)	54 (39-65)	65 (48-77)	0.045
Groups			
15-49	51 (38.3)	8 (25.0)	0.034
50-64	47 (35.3)	8 (25.0)	
≥65	35 (26.3)	16 (50.0)	
Sex female	62 (46.6)	19 (59.4)	0.195
Comorbidities			
Any	60 (45.1)	24 (75.0)	0.002
No. of comorbidities	0 (0-1)	2 (1-3)	0.002
Disease severity[b]			
Non-severe group	112 (84.2)	27 (84.4)	0.982
Severe group	21 (15.8)	5 (15.6)	
Outcomes			
Days of imaging tests changing to negative (-)	9 (7-13)	12 (4-20)	0.501
Days of nucleic acid tests changing to negative (-)	6 (4-7)	8 (4-12)	0.926
Death	17 (12.8)	7 (21.9)	0.004
Recovered	111 (83.5)	19 (59.4)	
Staying in hospital/transferred to another hospital	5 (3.8)	6 (18.8)	

Data are presented as No. (%) or median (IQR). [a], intestinal microecological regulators was defined as Anatomical Therapeutic Chemical (ATC) classification codes started with A07F. [b], the patient's baseline condition was classified into four levels according to the guidelines: mild, general, severe, critical severe, respectively, the first two levels were further classified as a non-severe subgroup and the latter two as a severe subgroup. IQR, interquartile range.

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Table S12 Baseline features of all patients with coronavirus disease 2019 (COVID-19) who started treatment with or without immunoglobin

Features	Immunoglobin[a]		P value
	Without (n=140)	With (n=25)	
Age (y)			
Median (IQR)	55 (42-67)	59 (43-66)	0.389
Groups			
15-49	50 (36.5)	9 (32.1)	0.906
50-64	45 (32.8)	10 (35.7)	
≥65	42 (30.7)	9 (32.1)	
Sex female	72 (52.6)	9 (32.1)	0.049
Comorbidities			
Any	69 (50.4)	15 (53.6)	0.757
No. of comorbidities	1 (0-2)	1 (0-2)	0.738
Disease severity[b]			
Non-severe group	117 (85.4)	22 (78.6)	0.395
Severe group	20 (14.6)	6 (21.4)	
Outcomes			
Days of imaging tests changing to negative (-)	9 (6-13)	11 (7-14)	0.501
Days of nucleic acid tests changing to negative (-)	6 (5-8)	5 (3-10)	0.624
Death	23 (16.8)	1 (3.6)	0.012
Recovered	108 (78.8)	22 (78.6)	
Staying in hospital/ transferred to another hospital	6 (4.4)	5 (17.9)	

Data are n (%) or median (IQR). [a], immunoglobin was defined as Anatomical Therapeutic Chemical (ATC) classification codes started with J06BA. [b], the patient's baseline condition was classified into four levels according to the guidelines: mild, general, severe, critical severe respectively, the first two levels were further classified as a non-severe subgroup and the latter two as a severe subgroup. IQR, interquartile range.

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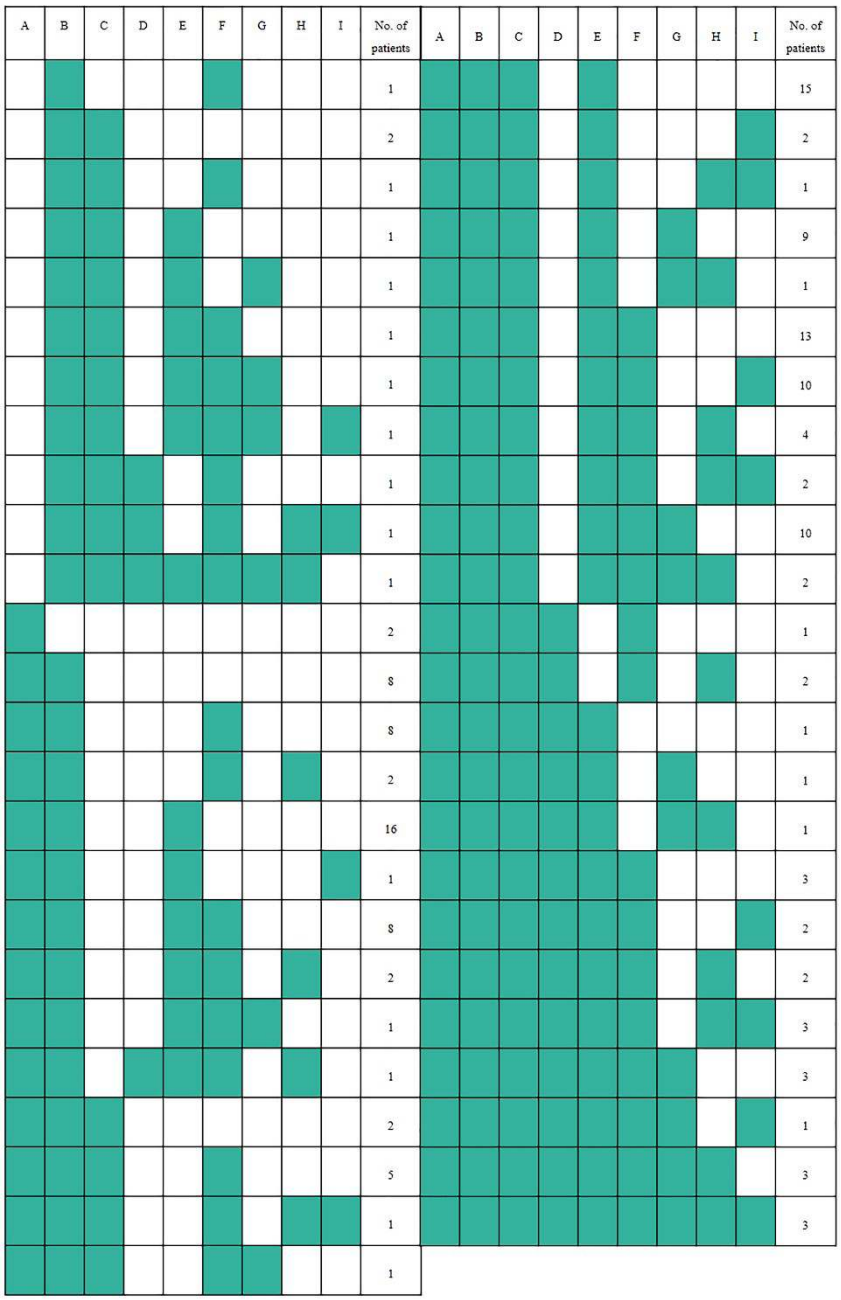

Figure S1 Medication combinations of 165 patients with coronavirus disease 2019 (COVID-19). The column with green color means with that specific medication. A. antivirals [Anatomical Therapeutic Chemical (ATC) classification codes started with J05]. B. antibacterials (J01). C. glucocorticoids (H02AB). D. antimycotics (J02). E. general nutrients (V06). F. traditional Chinese medicine (TCM, identified using drug name). G. vasoactive drugs (C01DA, C01CA, C04AB01). H. intestinal microecological regulators (A07F). I. immunoglobin (J06BA).

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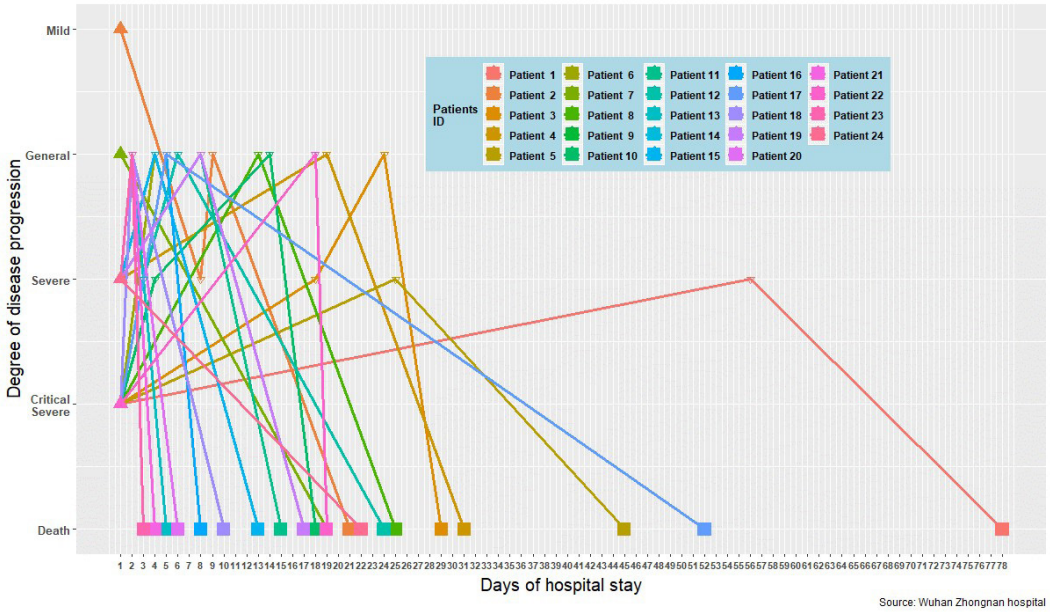

Figure S2 Disease progression of 24 death patients with coronavirus disease 2019 (COVID-19) by days of hospital stay. This figure presented the disease progression of 24 death patients since baseline. The patient's baseline condition was classified into four levels according to the guidelines "Diagnostic and treatment protocol for Novel Coronavirus Pneumonia (trial fifth version)": mild, general, severe, critical severe, respectively.

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