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.
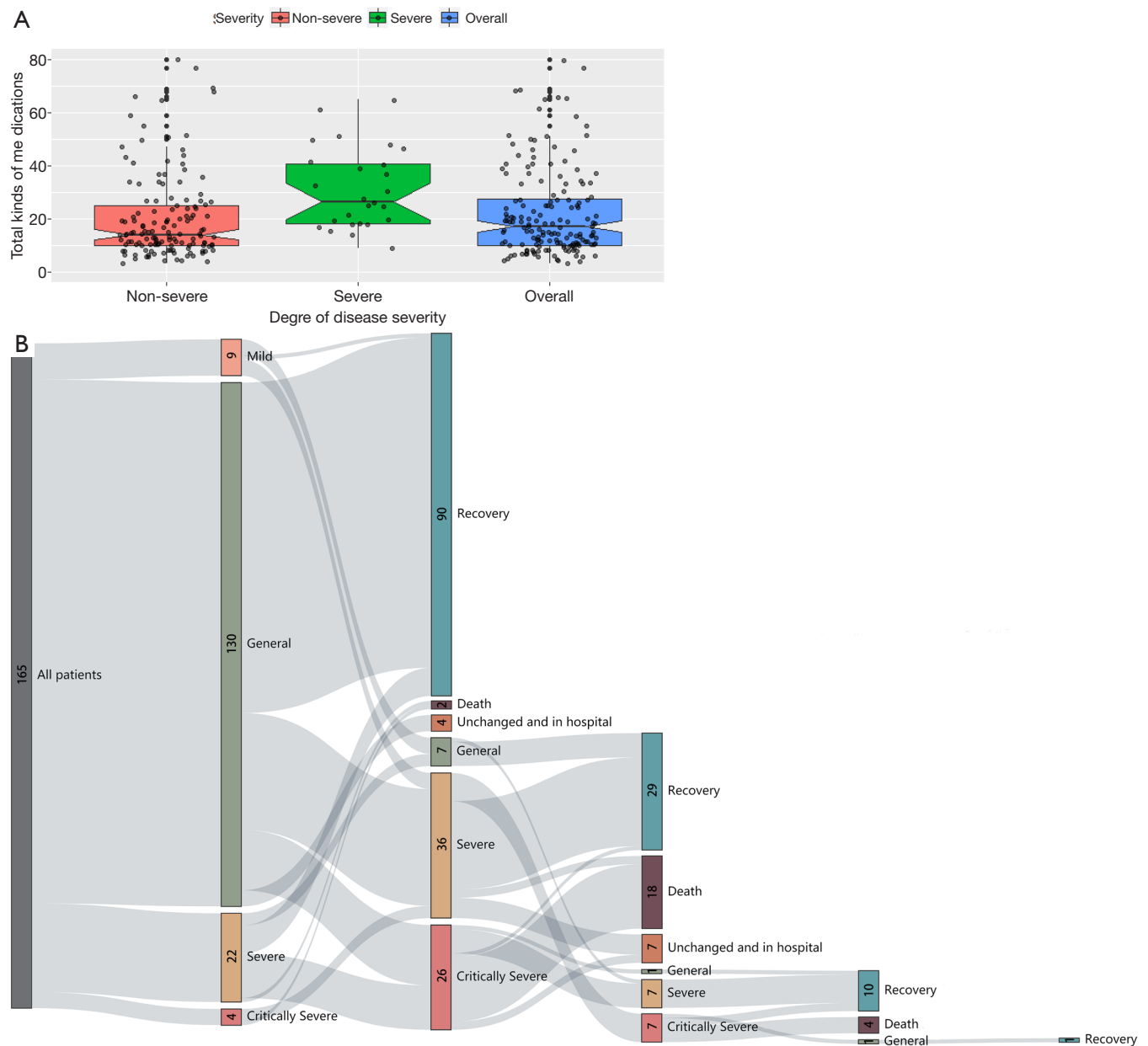
Figure 1 The total kinds of medications and disease progression for 165 patients with coronavirus disease 2019 (COVID-19). (A) The total kinds of medications grouped by disease severity and comorbidities. Total kinds of medications refer to the medications (generic names) per person used during the whole 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

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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

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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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Footnote

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