Incidence of Adverse Drug Reactions in COVID-19 Patients in China: An Active Monitoring Study by Hospital Pharmacovigilance System

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To evaluate the incidence, type, and risk factors associated with adverse drug reactions (ADRs) among patients with coronavirus disease 2019 (COVID-19) by Hospital Pharmacovigilance System (CHPS). A retrospective analysis was performed on 217 patients with COVID-19 admitted to the First Hospital of Changsha in China, from January 17, 2020, to February 29, 2020. The active monitoring model in CHPS was used to detect ADR signals of the hospital information system. The risk factors for the ADRs were classified using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system. Univariate and multivariate logistic regressions were carried out to analyze the risk factors of ADRs. Our results showed that the prevalence of ADRs was 37.8% in the patients, which was predominated by drug-induced gastrointestinal disorders and liver system disorders (23.0% vs. 13.8%). The ADR could be explained by the use of lopinavir/ ritonavir and umifenovir by 63.8% and 18.1%, respectively. There were 96.8% of ADRs that occurred within 14 days of hospitalization. Multivariable analysis showed that length of stay (odds ratio (OR): 2.02; 95% confidence interval (CI) 1.03–3.96; *P* = 0.04), number of drugs used in the hospital (OR: 3.17; 95% CI 1.60–6.27; *P* = 0.001) and underlying basic diseases (OR: 2.07; 95% CI 1.02–4.23; *P* = 0.04) were independent risk factor for ADRs in the patients. Together, the incidence of ADRs was significantly high during the treatment period. Moreover, the active monitoring of the CHPS system reflected ADRs during COVID-19 treatment in the real world, which provided reference for safe medication in the clinic.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The novel coronavirus pneumonia epidemic is quite serious, and has spread worldwide. The treatment scheme is still in the exploratory stage for coronavirus disease 2019 (COVID-19). However, little is known about the incidence of adverse drug reactions (ADRs) in patients with COVID-19.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The aim was to evaluate the incidence, type, and risk factors associated with ADRs among patients with COVID-19 by the Hospital Pharmacovigilance System (CHPS).

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The prevalence of ADRs was high in the 217 patients with COVID-19, the majority of the ADRs were drug-induced gastrointestinal disorders and liver system disorders. Length of stay, number of drugs used in the hospital, and underlying basic diseases were the independent risk factors for the occurrence of ADRs in patients with COVID-19.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The active monitoring of the CHPS system reflected the adverse reactions of patients with COVID-19 in the real world, which provided reference for clinical safe medication.

In late December 2019, a cluster of cases with severe acute respiratory syndrome 2019 novel coronavirus pneumonia (SARS-CoV-2) infection in Wuhan, China, aroused worldwide concern.[1] As of March 9, 2020, over 100 countries reported laboratory-confirmed cases of coronavirus disease 2019 (COVID-19), and > 110,000 cases have been diagnosed, with an estimated mortality risk of ~ 3%.[2]

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Received March 13, 2020; accepted April 20, 2020. doi:10.1002/cpt.1866

Unfortunately, no drug or vaccine has yet been approved to treat SARS-CoV-2 infection.[3] Lopinavir/ritonavir, interferon, umifenovir, chloroquine, remdesivir, favipiravir, anti-inflammatory drugs (such as corticosteroids and other molecules), Chinese traditional medicines, such as ShuFengJieDu capsules and Lianhuaqingwen capsules, Xuebijing injections are potential options for the treatment of novel CoV.[3–5] However, the treatment scheme is still in the exploratory stage.

A report[6] showed that the treatments were complex in co-combination patients with COVID-19 with basic diseases. The risk for drug-related adverse reactions is increased. At present, the recommended drugs, such as HIV protease inhibitors, have complex interactions,[7] interferon usage is special,[8] ribavirin has relatively more adverse reactions,[9] wheres no evidence is available for the use of umifenovir,[10] chloroquine,[11] and remdesivir.[12] Therefore, drug safety cannot be ignored while ensuring efficacy. Adverse drug reactions (ADRs) range from mild to life-threatening with short-term and long-term effects. However, little is known about the incidence of ADRs in patients with COVID-19.

The China Hospital Pharmacovigilance System (CHPS)[13] was developed by China National Center for Adverse Drug Reaction Monitoring (CNCAM) to collect and analyze information automatically extracted from sentinel hospitals. It may partially solve the problems of under-reporting, undue delays, and miscommunication. Better reporting systems can also have a positive effect on rational drug use in medical institutions. The real drug safety data were extracted to provide decision-making basis for drug risk management.

In this study, to investigate the ADRs of the patients in the real world, we used the CHPS system to actively monitor the medication safety of patients with COVID-19, which provide reference for clinically safe medication.

METHODS

Study design and population

A retrospective study was carried out in this study. Two hundred seventeen patients with COVID-19 who were transferred from the hospitals in Changsha to the First Hospital of Changsha, the designated hospital, from January 17 to February 29, 2020, were enrolled. Cases of COVID-19 were diagnosed according to the World Health Organization (WHO) interim guidance for all the patients. The study was approved by Ethics Committee of the First Hospital of Changsha and written informed consent was waived because of the retrospective nature of the study. All patients were codified and anonymized to protect the confidentiality of individual participants. After data coding and analysis, all records were deleted to further protect participants' confidentiality.

Active monitoring

All treatments used in the patients with COVID-19 were selected in the study, then through the literature, instructions of the US Food and Drug Administration (FDA), and global trigger tool white paper to establish the trigger items for depression in patients (**Table 1**). A retrospective chart review of a sample of 217 patients with COVID-19 transferred from the hospitals in Changsha to the designated hospital from January 17 to February 29, 2020, was carried out. All the medical records with identified triggers to determine the presence of ADRs by the active monitoring model in CHPS were used. Two clinical pharmacists checked the medical records of the system alarm cases one by one for relevance evaluation.

Table 1 The trigger items for active monitoring of ADR in inpatients with COVID-19

No.	Trigger items	Explanation
	Laboratory parameters	
L1	Platelet count < 3.5×10^9/L	Drug-induced platelet reduction
L2	Serum ALT or AST > 2 × ULN/serum TBil to > 2 × ULN/ALP ≥ 2 ULN	Drug-induced liver injury
L3	Serum cholesterol > 6 mmol/L	Drug-induced hypercholesterolemia
L4	Serum triglycerides > 1.7 mol/L	Drug-induced hyperlipidemia
L5	Electrocardiogram QT prolongation > 500 ms	Drug-induced QT prolongation
	Signature drug	
D1	Chlorethamine/Malay acid chlorobenzene/left sitiliquin/dexamison/heteropropion/sodium sulfate/calcium gluconate	Drug-induced allergies
D2	Metoclopramide/ondansetron/montmorillonite powder/lactose	Drug-induced gastrointestinal reactions
D3	Adrenaline	Drug-induced allergic shock
D4	Glutathione/magnesium isoglycyrrhizinate/JiangMeiLing capsule	Drug-induced liver injury
	Clinical symptoms	
S1	Itching of the skin/rash/urticaria/photosensitive reaction	Drug-induced skin and appendages disorders
S2	Anxiety/irritability	Drug-induced psychiatric disorders
S3	Dizziness/headache/fatigue	Drug-induced central nervous system disorders
S4	Loss of appetite/nausea/vomiting/abdominal pain/diarrhea/pancreatitis	Drug-induced gastrointestinal disorders
S5	Tinnitus/hearing loss	Drug-induced hearing disorders
S6	Blurred vision/eye discomfort	Drug-induced vision disorders
S7	Myalgia/joint pain	Drug-induced muscle-skeletal system disorders
S8	Sexual dysfunction/menstrual disorders	Drug-induced the reproductive system disorders

Data collection

The characteristics of the patients with COVID-19 (time of admission, length of stay, sex, age, basic diseases, etc.), history of drug allergies, the Antiviral Protocol, and the number of medications used during hospitalization were extracted. ADRs were evaluated when the trigger was positive. Then, the causality, the time of occurrence, suspicious drugs, and clinical outcome of ADRs were recorded.

Case assessment

Causality assessment was performed for all suspected ADRs using the WHO-Uppsala Monitoring Centre (WHO-UMC) system.[14] The WHO-UMC system is a universally accepted method for causality assessment.[15]

The relationship between the reported ADRs and drugs was categorized as certain, probable, possible, unlikely, conditional/unclassified, or unassessable/unclassifiable. Only cases categorized as certain, probable, and possible were included.

Seriousness of the identified suspected ADRs was determined according to the definition of the International Conference on Harmonization (ICH) E2A guideline (ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).[16] According to the ICH E2A guideline, a serious adverse event (AE) or reaction is any untoward medical occurrence that at any dose:

Resulted in death,
Is life-threatening,
Required hospitalization or resulted in prolongation of existing hospitalization,
Resulted in persistent or significant disability/incapacity, or
Caused congenital anomaly/birth defect or medically important event or reaction that required medical/surgical intervention to prevent serious outcome.

The clinical outcome indicators of ADRs generally include death, cured, improvement, recovered with sequelae, no healing, and unknown. The clinical cure of an ADR was considered when ADR symptoms disappeared or recovery of the abnormal indexes to normal values was observed.

Data processing and statistical analysis

Data were captured into a computer using an entry program developed with the WPS software package. Data were edited during and after data entry using WPS and SPSS 20. Both descriptive and analytical analyses were carried out on the data using SPSS. Both univariate and multivariate analyses were carried out to evaluate the associations of potential risk factors with the risk for ADRs. Results were presented as percentages and frequencies as appropriate. To test statistical significance, 95% confidence intervals (CIs) and/or *P* values were used. A P value < 0.05 was regarded as being statistically significant.

RESULTS

Characteristics of patients

Two hundred seventeen patients were included in this study (**Table 2**). Of the 217 patients, 111 (51.2%) were women and 106 (48.8%) were men. The mean age was 45.7 ± 16.6 years. There were 28.6% of them who had underlying basic diseases (hypertension, cardiovascular disease, cerebrovascular disease, diabetes, cancer, chronic kidney disease, chronic liver disease, HIV, and chronic obstructive pulmonary disease).

Of the 217 patients, 118 patients showed positive triggers, and 36 patients were excluded because the positive trigger was due to

Table 2 Characteristics of patient between those with ADRs and without ADRs

Characteristic	All Patients (*n* = 217)	Patients without ADRs (*n* = 135)	Patients with ADRs (*n* = 82)	*P* value
Age, years	45.7 ± 16.6	46.0 ± 16.2	45.2 ± 17.5	0.755
Length of stay	17.9 ± 8.33	15.9 ± 7.52	21.1 ± 8.63	*< 0.001*
Number of drugs used in the hospital	6.60 ± 3.05	5.40 ± 2.10	8.57 ± 3.34	*< 0.001*
Patient sex				
Male	106 (48.8%)	69 (51.1%)	37 (45.1%)	0.392
Female	111 (51.2%)	66 (48.9%)	45 (54.9%)	
History of drug allergies				
Yes	10 (4.6%)	3 (2.2%)	7 (8.5%)	*0.044*
No	207 (95.4%)	132 (97.8%)	75 (91.5%)	
Underlying basic diseases				
Yes	62 (28.6%)	33 (24.4%)	29 (35.4%)	0.084
No	155 (71.4%)	102 (75.6%)	53 (64.6%)	
Combined use of antiviral agent				
Yes	163 (75.1%)	95 (70.4%)	68 (82.9%)	*0.038*
No	54 (24.9%)	40 (29.6%)	14 (17.1%)	
Severe COVID-19				
Yes	50 (23.0%)	26 (19.3%)	24 (29.3%)	*0.090*
No	167 (27.6%)	109 (80.7%)	58 (70.7%)	

Data are *n* (%) or mean (+SD). *P* value in italic shows that the variables are statistically significant. Underlying basic diseases included hypertension, cardiovascular disease, cerebrovascular disease, diabetes, malignant tumor, chronic kidney disease, chronic liver disease, HIV, and chronic obstructive pulmonary disease. Severe COVID-19 was mainly defined according to the Diagnosis and Treatment of Novel Coronavirus Pneumonia (revised version fifth) by the General Office of The National Health Commission of People's Republic of China, Office of National Administration. Patients with severe COVID-19 refer to patients with clinical classification of severe and critical types.

the disease itself. A total of 94 ADRs were identified in 82 patients. The incidence rate of ADRs was 37.8%. One hundred nineteen patients (54.8%) used umifenovir, 179 patients (82.5%) used lopinavir/ritonavir, and 37 patients (17.1%) used chloroquine.

The mean age of the patients without ADRs (No ADR) group and with ADRs groups was 46.0 ± 16.2 and 45.2 ± 17.5 years, respectively. Compared with the No ADRs group, the length of stay (21.1 ± 8.63 vs. 15.9 ± 7.52; $P < 0.001$) was significantly longer in the ADRs group. The number of drugs used in the hospital (8.57 ± 3.34 vs. 5.40 ± 2.10; $P < 0.001$), history of drug allergies (3 (2.2%) vs. 7 (8.5%); $P < 0.044$), and combined use of antiviral agents (95 (70.4%) vs. 68 (82.9%); $P < 0.044$) were significantly higher in the ADRs group. There were no significant differences in the proportions of sex and underlying basic diseases between the two groups.

Risk factors for ADRs in patients with COVID-19

To identify risk factors associated with the occurrence of ADRs for the patients with COVID-19, a retrospective study was conducted. Univariate analysis showed that the following factors were extensively associated with the occurrence of ADRs: length of stay, combined use of antiviral agents, number of drugs used in the hospital, and history of drug allergies.

The results of the multivariate analysis were shown in **Table 3**: the independent risk factors for the occurrence of ADRs in patients with COVID-19 were length of stay (odds ratio (OR): 2.02; 95% CI 1.03–3.96; $P = 0.04$), number of drugs used in the hospital (OR: 3.12; 95% CI 1.60–6.27; $P = 0.001$) and underlying basic diseases (OR: 2.07; 95% CI 1.02–4.23; $P = 0.045$).

Characteristics of ADRs

Drug-related adverse reactions, as categorized by the system used, and the onset times are listed in **Tables 4 and 5**, respectively. Gastrointestinal (GI) disorders (23.0%) were the most frequent ADRs, followed by liver disorders (13.8%), skin and appendages disorders (4.15%), and hyperlipemia (1.38%).

Three cases of hyperlipidemia were caused by lopinavir/ritonavir. One case was a 37-year-old male patient with normal blood lipids before admission. On February 9, he was given lopinavir/ritonavir. The triglyceride value was 6.35 and 12.0 mmol/L on February 10 and 14, respectively. On February 14, the patient stopped using lopinavir/ritonavir. On February 19, the triglyceride was 10.3 mmol/L. Therefore, the patient was given fenofibrate capsules on the same day. The triglyceride decreased to 4.62 mmol/L until February 22. It was worth noting that two of the three cases of hyperlipidemia were in children.

In terms of time of onset of the ADRs, 9.57% (rash, diarrhea, and vomiting) occurred within the first day of treatment, 79.8% occurred within 7 days of treatment, and 96.8% occurred within 14 days of treatment.

Suspected drugs with ADRs are listed in **Table 6** and **Table S1**. Most of the reactions were associated with lopinavir/ritonavir and umifenovir with 63.8% and 18.1%, respectively. Chloroquine and antibacterial drugs were similar in causing ADRs with incidence of 5.31% and 4.25%, respectively. Of these, only 6.38% were found to be serious. The causal relationship assessed by using the WHO-UMC system in the suspected ADR cases were found to be probable and possible (55.3% vs. 44.7%). The prognosis of ADRs in these patients were favorable, with 62.8% cured and 37.2% improved.

DISCUSSION

Few studies regarding drug safety monitoring are reported in patients with COVID-19. Only one study[17] in China reported diarrhea associated with lopinavir/ritonavir use in patients with COVID-19. The study showed that after using lopinavir/ritonavir in 33 patients with COVID-19 in the Nanchong area in China, 15 patients had diarrhea, rash, and other ADRs, the incidence was 42.9%. In our study, we used the CHPS system to actively monitor the drug safety issues of patients with COVID-19 for the first time. This ADR monitoring system has improved work efficiency and the frequency of ADR reporting. It may partially solve the problem of under-reporting, undue delays, and miscommunication, and better reflect the ADRs for patients with COVID-19 in the real world.[13] Our study showed that ADRs in patients with COVID-19 were mainly characterized by GI reactions, liver injury, rash, and hyperlipidemia, with

Table 3 Univariate and multivariate analysis of risk factor for ADRs in patients with COVID-19

Variables	Patients with No ADRs (n = 135)	Patients with ADRs (n = 82)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	P value	OR (95% CI)	P value
Age, years	41 (2–84)	45 (1–78)	0.938 (0.542–1.62)	0.820	0.511 (0.259–1.01)	0.052
Male	69 (51.1%)	37 (45.1%)	1.27 (0.733–2.20)	0.392	—	—
Length of stay	14 (5–36)	20 (5–39)	3.42 (1.93–6.08)	*< 0.001*	2.02 (1.03–3.96)	*0.04*
Combined use of antiviral agent	95 (70.4%)	68 (82.9%)	2.04 (1.03–4.05)	*0.040*	—	—
Number of drugs in the hospital	5 (2–11)	9 (3–14)	3.99 (2.23–7.13)	*< 0.001*	3.17 (1.60–6.27)	*0.001*
History of drug allergies	3 (2.22%)	7 (8.54%)	4.11 (1.03–16.3)	*0.045*	3.67 (0.83–16.2)	0.085
Underlying basic diseases	33 (24.4%)	29 (35.4%)	1.69 (0.929–3.08)	0.086	2.07 (1.02–4.23)	*0.045*
Severe COVID-19	26 (19.3%)	24 (29.3%)	1.73 (0.915–3.29)	0.091	—	—

Data are n (%) or median (interquartile range). P value in italic shows that the variables are statistically significant. ADRs, adverse drug reactions; CI, confidence interval; COVID-19, coronavirus disease 2019; OR, odds ratio.

Table 4 Involved organs and systems of ADRs for the patients with COVID-19

The system involved	Incidence of ADRs (%)
Skin and appendages disorders	9 (4.15)
Rash	8 (3.69)
Pruritus	1 (0.46)
Skin discoloration	1 (0.46)
Gastrointestinal disorders	50 (23.0)
Nausea	13 (5.99)
Nausea, vomiting	8 (3.69)
Nausea, vomiting, diarrhea	2 (0.92)
Diarrhea	19 (8.76)
Vomiting	7 (3.22)
Vomiting, diarrhea	1 (0.46)
Liver and biliary system disorders	30 (13.8)
SGPT increased	30 (13.8)
Metabolic and nutritional disorders	
Hyperlipemia	3 (1.38)
Central nervous system disorders	
Headache	1 (0.46)
Total	94 (43.3)

Data are *n* (%). Frequency was calculated as number/217*100%.
ADRs, adverse drug reactions; COVID-19, coronavirus disease 2019; SGPT, serum glutamic pyruvic transaminase.

incidence of 23.0%, 13.8%, 4.15%, and 1.38%, respectively. There were 96.8% of ADRs that occurred within 14 days. GI reactions occurred earlier, usually within 7 days. The proportion of ADRs (63.8%) caused by lopinavir/ritonavir was highest. The incidence of ADRs by lopinavir/ritonavir was 33.5% (60/179), which was lower than the Yang *et al*. study.[17] The difference might be explained by the small sample size in the Yang *et al*. study.[17] The results of other studies are slightly different, which may be related to the inconsistency of the study population. The safety monitoring data of other studies are mainly concentrated in patients with AIDS and healthy people.[18,19] For example, as seen in the Gonzalez-Garcia *et al*. study, the most frequently reported AE in healthy adult subjects was diarrhea (26/40; 65%).[18] A randomized trial to evaluate the efficacy and safety of lopinavir/ritonavir in the treatment of HIV-1 infection reported that the incidence of diarrhea in moderate/severe AEs was 16%.[19]

The incidence of adverse reactions by umifenovir and chloroquine were 17 of 119, 14.3% vs. 5/37, 13.5% respectively, mainly manifested as GI reaction and liver injury. Decrease in vision or cardiotoxicity was not observed in patients using chloroquine.[20,21] This is because chloroquine induces visual toxicity that is generally associated with long-term use. However, the duration of treatment by chloroquine in patients with COVID-19 was generally < 10 days in our study.

After symptomatic support treatment, all the ADRs turned out well, 62.8% were cured, and 37.2% were improved. In all the ADRs

Table 5 Frequency of ADRs for the patients with COVID-19 according to the time of onset

	The time interval between drug administration and the onset of ADRs, days				
ADRs	**≤1**	**1–3**	**4–7**	**8–14**	**> 14**
Skin and appendages disorders					
Rash	2 (2.13)	1 (1.06)	2 (2.13)	3 (3.19)	0
Pruritus	0	0	0	0	1 (1.06)
Skin discoloration	0	1 (1.06)	0	0	0
Gastrointestinal disorders					
Nausea	0	2 (2.13)	9 (9.57)	2 (2.13)	0
Nausea, vomiting	0	3 (3.19)	4 (4.25)	1 (1.06)	0
Nausea, vomiting, diarrhea	0	2 (2.13)	0	0	0
Diarrhea	1 (1.06)	7 (7.45)	8 (8.51)	2 (2.13)	1 (1.06)
Vomiting	1 (1.06)	4 (4.25)	1 (1.06)	1 (1.06)	0
Vomiting, diarrhea	0	1 (1.06)	0	0	0
Liver and biliary system disorders					
SGPT increased	0	8 (8.51)	10 (10.6)	11 (11.7)	1 (1.06)
Metabolic and nutritional disorders					
Hyperlipemia	0	1 (1.06)	1 (1.06)	1 (1.06)	0
Central nervous system disorders					
Headache	0	0	1 (1.06)	0	0
Total	4 (9.57)	30 (31.9)	36 (38.3)	21 (22.3)	3 (3.19)

Data are *n* (%). ADRs are presented as individual symptoms and system organ class, based on the MedDRA classification. Frequency was calculated as number/94*100%.
ADR, adverse drug reaction; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; SGPT, serum glutamic pyruvic transaminase.

Table 6 Suspicious drugs, casualty assessment, and prognosis of ADRs for the patients with COVID-19

	ADRs		Casualty assessment		Prognosis	
Suspicious drugs	**All ADRs**	**SADRs**	**Probable**	**Possible**	**Cure**	**Improvement**
Umifenovir	17 (18.1)	6 (6.38)	5 (5.31)	12 (12.8)	5 (5.31)	12 (12.8)
Lopinavir and ritonavir	60 (63.8)	10 (10.6)	35 (37.2)	25 (26.6)	44 (20.3)	16 (17.0)
Chloroquine	5 (5.31)	0	4 (4.25)	1 (1.06)	4 (4.25)	1 (1.06)
Xuebijing injection	3 (3.19)	1	2 (2.13)	1 (1.06)	2 (2.13)	1 (1.06)
Antibacterial drugs	4 (4.25)	0	2 (2.13)	2 (2.13)	1 (1.06)	3 (3.19)
Other drugs	5 (5.31)	0	4 (4.25)	1 (1.06)	3 (3.19)	2 (2.13)
Total	94 (100.0)	17 (18.1)	52 (55.3)	42 (44.7)	59 (62.8)	35 (37.2)

Data are *n* (%). Frequency was calculated as number/94*100%.
ADRs, adverse drug reactions; COVID-19, coronavirus disease 2019; SADRs, serious adverse drug reactions.

observed, serious adverse reactions accounted for 18.1%, mainly liver injury and hyperlipidemia. For the 17 patients with serious adverse reactions, 14 had liver injury and 3 had hyperlipidemia. Hypertriglyceridemia and hypercholesterolemia were the most frequently observed laboratory abnormalities in lopinavir/ritonavir recipients in clinical trials and may be the reason for discontinuation of therapy in some patients.[22] Increases in total cholesterol and triglycerides were seen within the first month of starting therapy and were relatively stable then after.[23] In our study, three cases of hyperlipidemia caused by lopinavir/ritonavir were noted. It is worth noting that two of the three cases of hyperlipidemia were in children. In the process of clinical use, it is necessary to closely monitor the changes of blood lipids in pediatric patients.

Because ADRs are the single most common reason for poor adherence to treatment, identification of risk factors for the occurrence of ADRs is essential to optimize the initial choice of antiretroviral regimen before initiating therapy and to adapt the pace of surveillance to each unique situation. Our study showed that the independent risk factors for the occurrence of ADRs in patients with COVID-19 included length of stay (OR: 2.02; 95% CI 1.03–3.96; $P = 0.04$), number of drugs used in the hospital (OR: 3.17; 95% CI 1.60–6.27; $P = 0.001$), and underlying basic diseases (OR: 2.07; 95% CI 1.02–4.23; $P = 0.045$). One study observed that the ADR was significantly associated with the number of drugs and urgent hospital admission.[24] However, most patients were admitted through outpatient service in our study, so the factor of urgent hospital admission was not involved. Polypharmacy has been reported to be a strong risk factor for ADR in several studys.[25] The length of stay was reported to be significantly associated with the occurrence of ADRs in univariate analysis in the Kojima *et al.* study.[24] In addition, there is also significant association between the age and the occurrence of ADR, but this was not observed in our study. Although other studies have associated age as a risk factor for ADR,[26] our study did not show any association between age and ADRs.

The interpretation of these results is limited to the context from which participants were drawn. The randomized controlled trial cohort consisted of patients from health facilities in Hunan Province and may not be representative of patients across China. In addition, partial evaluation of possible ADR does not completely exclude the influence of disease. However, in our study, we try our best to avoid the interference caused by the COVID-19 infection. Patients with abnormal indicators or related symptoms and diseases before admission cannot be judged as an ADR according to the evaluation criteria of ADRs. Furthermore, we only observed adverse reactions during hospitalization. However, late-cut retinopathy caused by chloroquine may occur many years after discontinuation of the treatment. So further studies with more extended follow-up periods are needed to assess the longer-term implications of AEs and the potential fluidity in predictors of such events.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

ACKNOWLEDGMENTS

The authors thank the medical staff at the front line of the epidemic for their observation of the adverse reactions during the treatment of patients with COVID-19.

FUNDING

The research is supported by Hunan Provincial Science and Technology Major Project (No. 2020SK3014), the scientific research project of Hunan Health Commission (No. 20200202), and Natural Science Foundation of Hunan Province (No. 2017JJ2285).

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

J.S., X.P.C., G.F.H., and J.Y.L. wrote the manuscript. J.S., X.Y.D., J.J.H., and G.F.H. designed the research. J.S., S.Q.H., and Y.L. performed the research. J.S., S.Q.H., Y.L. and J.H.F. analyzed data.

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