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Virus Research 294 (2021) 198262

Contents lists available at ScienceDirect

Virus Research

journal homepage: www.elsevier.com/locate/virusres

A retrospective comparison of drugs against COVID-19

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ARTICLE INFO

Keywords:
Arbidol
Corticosteroids
Lopinavir/ritonavir
Hydroxychloroquine
Oseltamivir
COVID-19

ABSTRACT

Coronavirus disease 19 (COVID-19) has posed serious threats to the general population. To relieve the crisis, a comparison of drug effects against COVID-19 is instructive. Between January 27, 2020 and March 21, 2020, a total of 333 patients treated with arbidol, corticosteroids, hydroxychloroquine, lopinavir/ritonavir, or oseltamivir monotherapy, having definite outcomes and serological antibody detection results, were retrospectively analyzed. The hydroxychloroquine group had a significantly reduced duration of hospital stay than the arbidol and corticosteroids groups. The oseltamivir group had a significantly shorter length of hospital stay than the arbidol, corticosteroids, and lopinavir/ritonavir groups. The hydroxychloroquine group had a significantly higher IgM titer than the other four groups and exhibited significantly higher IgG levels than the arbidol, lopinavir/ritonavir, and oseltamivir groups. Our findings indicated that hydroxychloroquine might have the potential for efficient COVID-19 management, while oseltamivir should be prudently considered in combination therapy.

1. Introduction

Coronavirus disease 19 (COVID-19), for which the causative pathogen was later identified as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has swept the globe rapidly since its outbreak in December 2019. (Lu et al., 2020; Wu and McGoogan, 2020; Zhu et al., 2020b) This highly transmissible disease has involved more than 200 countries and territories and the pandemic has caused a Public Health Emergency of International Concern. (Li et al., 2020a; Lv et al., 2020) As of November 8, COVID-19 has infected 49,727,316 cases and caused a total of 1,248,373 deaths globally. (WHO, 2020)

Environmental factors such as temperature, wind speed, and forest coverage could affect the transmission and even prognosis of COVID-19. (Eslami and Jalili, 2020; Roviello and Roviello, 2020) To combat COVID-19 infection, several measures are taken to manage the epidemic. (Valle et al., 2020) The development of a vaccine or a new drug against SARS-CoV-2 is time-consuming. (Ahsan et al., 2020; Amanat and Krammer, 2020) Some vaccines show superior preventive efficiency, but are not available for the general population before the fulfilment of preclinical evaluations. (Tu et al., 2020; Zhu et al., 2020a) It takes at least 14 years before the final introduction of a new drug into the market from the research and development phase. (Ahsan et al., 2020) Under these circumstances, repurposing the already existing drugs provides an efficient approach to relieve the threats caused by COVID-19. (Guy et al., 2020) Arbidol, namely umifenovir, a derivative of indole carboxylic acids, is licensed for prophylaxis and treatment of influenza A and B and other respiratory viruses and functions mainly by blocking the virus-cell membrane fusion thereby preventing viral host cell entry. (Blaising et al., 2014) Arbidol exhibits antiviral efficiency towards globally prevalent pathogenic viruses including Ebola virus, human herpesvirus 8, and hepatitis C virus. (Pécheur et al., 2016) Arbidol has been used to treat COVID-19 infection since January 2020. (Deng et al., 2020) Corticosteroids have the potential to prevent an extended cytokine response and accelerate the resolution of pulmonary and systemic inflammation in pneumonia, (Russell et al., 2020) thus contributing to relieving the symptoms of SARS-CoV-2 infection. However, there are also some side effects. (Cheng et al., 2020) Chloroquine and hydroxychloroquine were designated as antimalarial drugs and have been demonstrated as potential broad-spectrum antiviral drugs. (Savarino et al., 2006) Hydroxychloroquine, one of the currently most commonly employed antirheumatic drugs, can inhibit the entry of viruses, prevent virus-cell fusion, and exert anti-inflammatory effects. (Hu

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https://doi.org/10.1016/j.virusres.2020.198262
Received 6 September 2020; Received in revised form 14 November 2020; Accepted 10 December 2020
Available online 14 December 2020

et al., 2017; Wang et al., 2020b) The drug effects of hydroxychloroquine against COVID-19 are controversial. (Chowdhury et al., 2020; Fihn et al., 2020) Lopinavir/ritonavir is highly potent in fighting against human immunodeficiency virus (HIV) infection and also demonstrates efficiency in treating SARS-CoV and MERS-CoV. (Corbett et al., 2002) To combat COVID-19, lopinavir/ritonavir was also repurposed. (Li et al., 2020b) Oseltamivir inhibits the spread of influenza virus in the human body by targeting the neuraminidase distributed on the surface of the virus and is approved for the treatment of influenza A and B. (McClellan and Perry, 2001) Many patients were treated with oseltamivir during the pandemic even before a definitive diagnosis. (Wang et al., 2020a) Many clinical trials were launched to evaluate the effects against SARS-CoV-2 of these candidate drugs either alone or in combination. (Chowdhury et al., 2020; Sanders et al., 2020) A comprehensive comparison of the therapeutic effects of these five drugs is therefore meaningful and instructive.

In this study, we retrospectively compared the therapeutic effects of arbidol, corticosteroids, hydroxychloroquine, lopinavir/ritonavir, and oseltamivir monotherapy against COVID-19. The drug effects were evaluated using the length of hospital stay and the serological levels of IgM and IgG. Comparisons of drug effects were performed in each two groups. The correlation between treatment time and drug effects was also analyzed to clarify the effects of different drugs.

2. Materials and methods

2.1. Data source

Among the 2044 COVID-19 patients hospitalized in the Optical Valley Campus and Sino-French New City Campus of Tongji Hospital, Wuhan, China, between January 27, 2020, and March 21, 2020, 831 patients with definite outcomes had serological antibody detection. (Liu et al., 2020) COVID-19 was diagnosed based on the Diagnosis and Treatment guidance of COVID-19 (7th edition) released by the National Health Commission of China. (Liu et al., 2020) To exclude the effects of combination therapies, only patients treated with arbidol, corticosteroids, hydroxychloroquine, lopinavir/ritonavir, or oseltamivir monotherapy were included in the analysis. Disease severity, symptoms, comorbidities, and outcomes were defined as reported previously. (Liu et al., 2020) The highest temperature was defined as the highest axillary temperature recorded during hospitalization. Before discharge, two consecutive negative SARS-CoV-2 nucleic acid detection results were necessary. The time interval from the first positive result to the confirmation of negative SARS-CoV-2 nucleic acid was defined as the negative conversion duration. This study was approved by the Research Ethics Commission of Tongji Hospital of Huazhong University of Science and Technology. All the procedures being performed were part of the routine care, and informed consent was waived. Patient data were extracted from electronic medical records, cross-checked for consistency before final data entry, and recorded in a computerized database.

2.2. Statistical analysis

Continuous variables were described using the mean and range, while categorical variables were presented as counts (percentages). For continuous variables, the differences between groups were compared using Student's *t*-test. Comparisons of the proportions of categorical variables were performed using the Chi-squared test or Fisher's exact test. Correlation analyses were conducted using Pearson's correlation test. Data were analyzed and plotted using GraphPad Prism 7 (GraphPad Software, San Diego, CA) and presented as the mean ± SEM. All statistical tests were two-sided, and $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Characteristics of patients

Between January 27, 2020 and March 21, 2020, COVID-19 patients, who had a definite outcome (discharge or death) and serological antibody detection results, were recruited. Eligible patients were those treated with monotherapy of arbidol, corticosteroids, hydroxychloroquine, lopinavir/ritonavir, or oseltamivir. A total of 333 patients were included in the study and subdivided into five groups: 277 cases were prescribed arbidol, 15 cases were treated with corticosteroids monotherapy, 8 cases received hydroxychloroquine, 14 patients were given lopinavir/ritonavir, and 19 cases received oseltamivir. Patient characteristics are summarized in Table 1. Overall, 136 male patients and 197 female patients were analyzed. Their ages ranged from 20 to 94 years old (mean, 59.52). A total of 222 patients had mild/moderate disease, 105 patients had severe disease, and 6 patients had critical disease. Only 5 patients were administered to the intensive care unit. Nearly all patients (95.80 %) had symptoms such as fever, cough, dyspnea, sputum, and fatigue. The highest axillary temperature ranged from 35.7 ℃ to 41.0 ℃ (mean, 37.89 ℃). A total of 136 cases were in general health, while 197 cases had comorbidities such as hypertension, diabetes, chronic heart disease, cancer, and chronic obstructive pulmonary disease. The mean negative conversion duration of SARS-CoV-2 nucleic acids was 26.31 days (from 1 day to 74 days). At the end of observation, only 3 patients had died.

When compared between the groups, the baseline characteristics were similar except for those of the corticosteroids group. The corticosteroids group tended to be older than the arbidol ($P = 0.0234$), hydroxychloroquine ($P = 0.0242$), and oseltamivir ($P = 0.0096$) groups. Compared with the arbidol group, the corticosteroids group had more sever disease ($P < 0.0001$), a higher ICU administration rate ($P < 0.0001$), a higher temperature ($P = 0.0292$), and a worse outcome ($P = 0.0072$). By comparison of the corticosteroids and oseltamivir groups, a higher proportion of the corticoids group had a more critical disease ($P = 0.0233$) and were hospitalized in ICU ($P = 0.0294$).

3.2. Effects of different drugs against COVID-19

The length of hospital stay can be used to perceive the therapeutic effects of drugs directly. (Chowdhury et al., 2020) Prescription of hydroxychloroquine or oseltamivir seemed to be capable of shortening the length of hospital stay (Fig. 1a). There was no statistically significant difference between the arbidol group and the corticosteroids group regarding the length of hospital stay ($P = 0.0792$) (Fig. 1b). The hydroxychloroquine group had a significantly reduced duration of hospital stay than the arbidol group ($P = 0.0384$) and the corticosteroids group ($P = 0.0007$), while no difference was found when compared with the lopinavir/ritonavir group ($P = 0.0600$) (Fig. 1c–e). The length of hospitalization in the lopinavir/ritonavir group and the arbidol group was not significantly different ($P = 0.9574$) (Fig. 1f). The same result was obtained when comparing the lopinavir/ritonavir group with the corticosteroids group ($P = 0.1738$) (Fig. 1g). Except for the hydroxychloroquine group ($P = 0.7766$), the oseltamivir group had a significantly shorter length of hospital stay than the arbidol ($P = 0.0004$), corticosteroids ($P = 0.0002$), and lopinavir/ritonavir ($P = 0.0223$) groups (Fig. 1h–k).

Detection of serological IgM and IgG against SARS-CoV-2 helps evaluate the severity and prognosis of COVID-19. (Hou et al., 2020) Hydroxychloroquine and oseltamivir demonstrated influences on serological IgM levels (Fig. 2a). The arbidol and corticosteroids groups had similar IgM levels ($P = 0.7497$) (Fig. 2b). The hydroxychloroquine group had a significantly higher IgM titer than the arbidol ($P = 0.0006$), corticosteroids ($P = 0.0077$), and lopinavir/ritonavir ($P = 0.0037$) groups (Fig. 2c–e). The IgM level of the lopinavir/ritonavir group showed no significant decrease compared with the arbidol ($P = 0.3717$) and

Table 1
Characteristics of patients.

Characteristics		Arbidol (n = 277)	Corticosteroids (n = 15)	Hydroxychloroquine (n = 8)	Lopinavir/ritonavir (n = 14)	Oseltamivir (n = 19)
Gender	male	116 (41.88 %)	3 (20.00 %)	1 (12.50 %)	10 (71.43 %)	6 (31.58 %)
	female	161 (58.12 %)	12 (80.00 %)	7 (87.50 %)	4 (28.57 %)	13 (68.42 %)
Age, range (mean), years		20–94 (59.60)	36–86 (68.20)	33–70 (54.13)	28–88 (60.07)	23–80 (53.37)
Disease severity	mild/moderate	192 (69.32 %)	4 (26.67 %)	4 (50.00 %)	8 (57.14 %)	14 (73.69 %)
	severe	83 (29.96 %)	8 (53.33 %)	4 (50.00 %)	6 (42.86 %)	4 (21.05 %)
	critical	2 (0.72 %)	3 (20.00 %)	0 (0.00 %)	0 (0.00 %)	1 (5.26 %)
ICU administration	yes	1 (0.36 %)	4 (26.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
	no	276 (99.64 %)	11 (73.33 %)	8 (100.00 %)	14 (100.00 %)	19 (100.00 %)
Symptoms	yes	264 (95.31 %)	15 (100.00 %)	8 (100.00 %)	13 (92.86 %)	19 (100.00 %)
	no	13 (4.69 %)	0 (0.00 %)	0 (0.00 %)	1 (7.14 %)	0 (0.00 %)
Highest temperature, range (mean), ℃		35.7–41.0 (37.84)	36.2–39.9 (38.42)	36.7–39.0 (38.54)	36.3–39.0 (37.87)	35.9–39.5 (37.97)
Comorbidities	yes	158 (57.04 %)	12 (80.00 %)	6 (75.00 %)	10 (71.43 %)	11 (57.89 %)
	no	119 (42.96 %)	3 (20.00 %)	2 (25.00 %)	4 (28.57 %)	8 (42.11 %)
Length of hospital stay, range (mean), days		4–46 (22.44)	16–51 (27.33)	11–20 (14.50)	4–44 (22.29)	4–35 (13.42)
Negative conversion duration of nucleic acids, range (mean), days		6–46 (23.43)	1–74 (26.06)	1–51 (28.94)	9–53 (28.40)	3–47 (30.00)
Outcome	discharge	276 (99.64 %)	13 (86.67 %)	8 (100.00 %)	14 (100.00 %)	19 (100.00 %)
	death	1 (0.36 %)	2 (13.33 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)

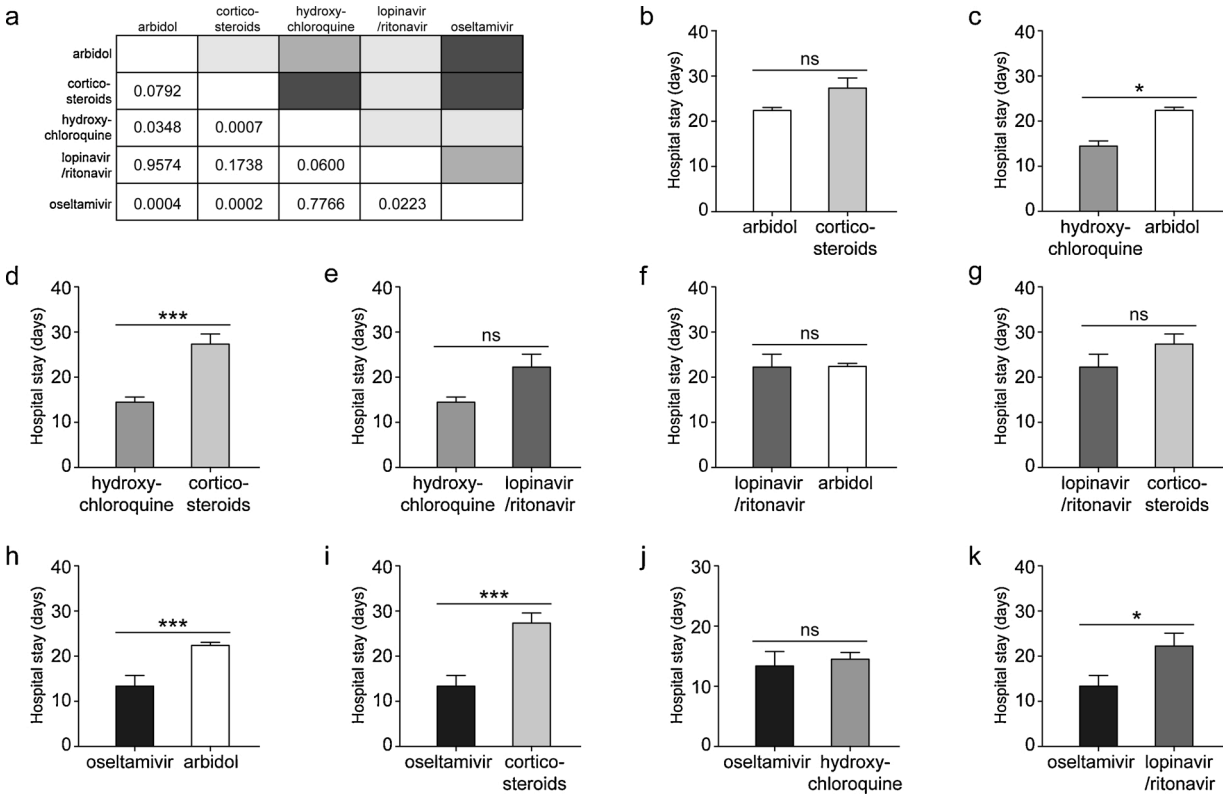

Fig. 1. Comparison of the length of hospital stay between different treatment groups. (a) Overall comparison of the length of hospital stay between different groups. *P* value was calculated and depicted. Grey color scale was used to describe the statistical significance. The darker the color, the greater the difference. Comparisons of hospitalization duration were performed in each two groups: (b) the arbidol and corticosteroids groups, (c) the hydroxychloroquine and arbidol groups, (d) the hydroxychloroquine and corticosteroids groups, (e) the hydroxychloroquine and lopinavir/ritonavir groups, (f) the lopinavir/ritonavir and arbidol groups, (g) the lopinavir/ritonavir and corticosteroids groups, (h) the oseltamivir and arbidol groups, (i) the oseltamivir and corticosteroids groups, (j) the oseltamivir and hydroxychloroquine groups, and (k) the oseltamivir and lopinavir/ritonavir groups. *P* value was calculated using two-sided Student's *t*-test, and denoted as * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$, "ns" represents "not significant".

corticosteroids ($P = 0.5750$) groups (Fig. 2f and g). The IgM titer of the oseltamivir group was significantly lower than that of the hydroxychloroquine group ($P = 0.0216$), while there was no statistically significant difference when compared with the other groups (arbidol, $P = 0.6983$; corticosteroids, $P = 0.5760$; lopinavir/ritonavir, $P = 0.2936$) (Fig. 2h–k). Hydroxychloroquine or oseltamivir might affect serological IgG titer (Fig. 3a). The IgG levels in the arbidol and corticosteroids groups did not show a significant difference ($P = 0.7450$) (Fig. 3b). The hydroxychloroquine group exhibited higher IgG levels than the arbidol ($P = 0.0154$) and lopinavir/ritonavir ($P = 0.0294$) groups, while there

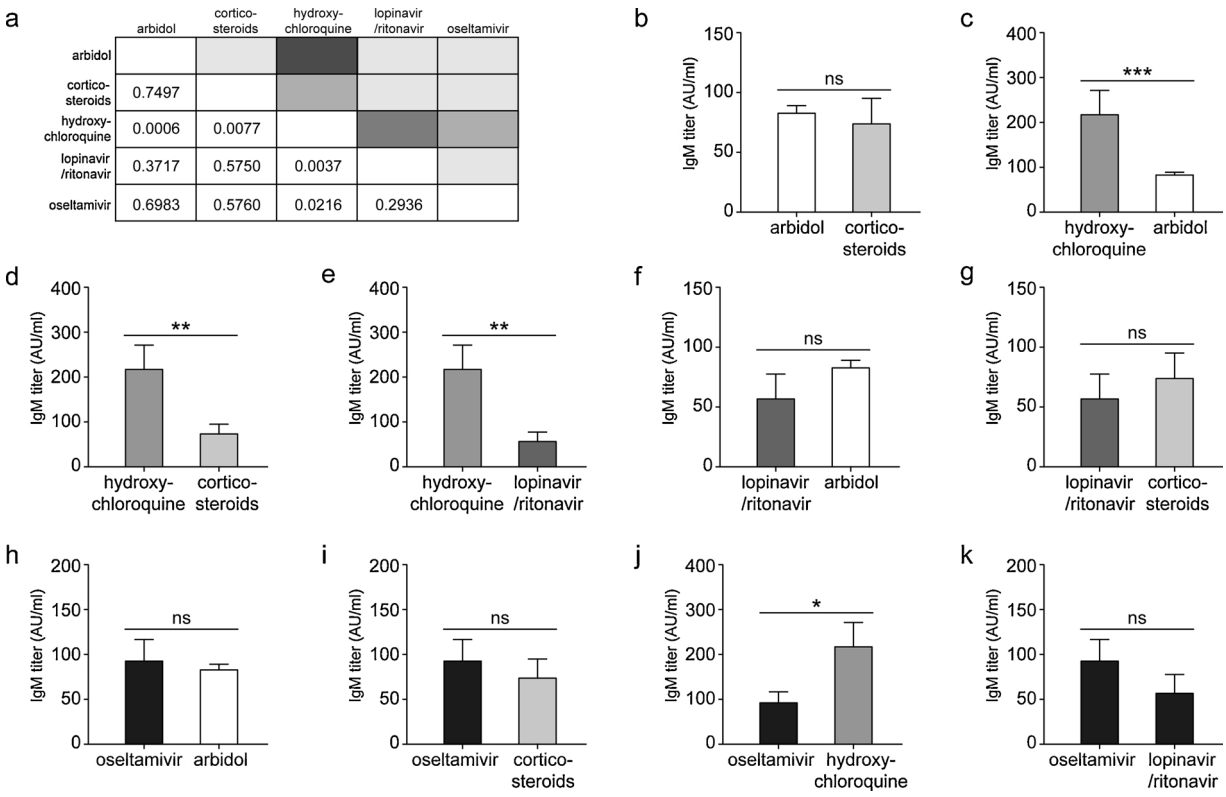

Fig. 2. Comparison of serological IgM titer between different treatment groups. (a) Overall comparison of serological IgM titer between different groups. *P* value was calculated and depicted. Grey color scale was used to describe the statistical significance. The darker the color, the greater the difference. Comparisons of serological IgM titer were performed in each two groups: (b) the arbidol and corticosteroids groups, (c) the hydroxychloroquine and arbidol groups, (d) the hydroxychloroquine and corticosteroids groups, (e) the hydroxychloroquine and lopinavir/ritonavir groups, (f) the lopinavir/ritonavir and arbidol groups, (g) the lopinavir/ritonavir and corticosteroids groups, (h) the oseltamivir and arbidol groups, (i) the oseltamivir and corticosteroids groups, (j) the oseltamivir and hydroxychloroquine groups, and (k) the oseltamivir and lopinavir/ritonavir groups. *P* value was calculated using two-sided Student's *t*-test, and denoted as * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$, "ns" represents "not significant".

was no significant difference between the hydroxychloroquine and corticosteroids ($P = 0.0822$) groups (Fig. 3c–e). The IgG titer of the lopinavir/ritonavir group was not significantly different from those of the arbidol ($P = 0.4015$) and corticosteroids ($P = 0.3394$) groups (Fig. 3f and g). The oseltamivir group had lower IgG titers than the arbidol ($P = 0.0062$), corticosteroids ($P = 0.0182$), and hydroxychloroquine ($P = 0.0015$) groups (Fig. 3h–j). However, the difference between the oseltamivir and lopinavir/ritonavir groups did not reach the predefined significance threshold ($P = 0.1971$) (Fig. 3k).

3.3. Correlation analyses of treatment time and drug effects

To further clarify the effects of different drugs, correlation analyses between treatment time and the mean length of hospital stay with the same treatment time were performed. There was no significant correlation between treatment time and mean hospital stay for any of the five drugs (Supplementary Fig. 1a–e). When analyzed in individual patients, the treatment times of none of the drugs correlated with the length of hospital stay (Supplementary Fig. 1f).

Similar results were obtained by correlation analyses of treatment time and the mean IgM or IgG titer. The treatment time of either drug had no significant correlation with the mean IgM titer of the same treatment time (Supplementary Fig. 2a–e). The treatment times of the drugs also did not correlate with individual IgM titers (Supplementary Fig. 2f). Similarly, no significant correlation was observed by correlation analyses of drug administration time and mean IgG level (Supplementary Fig. 3a–e). In individual cases, the drug treatment time had no significant correlation with the IgG titer (Supplementary Fig. 3f).

4. Discussion

The COVID-19 pandemic has posed serious threats to the general population and healthcare workers, bringing a great deal of pain and suffering. (WHO, 2020) In this retrospective analysis, we compared the therapeutic effects of arbidol, corticosteroids, hydroxychloroquine, lopinavir/ritonavir, and oseltamivir monotherapy against COVID-19. The hydroxychloroquine group had a shorter length of hospital stay than the arbidol and corticosteroid groups. Besides, the hydroxychloroquine group also exhibited significantly higher serological IgM and IgG levels than the other four groups. Therefore, it is reasonable to consider hydroxychloroquine an efficient candidate drug in treating COVID-19.

In the absence of definitive and specific drugs targeting SARS-CoV-2, drug repurposing is an efficient and promising approach to relieve distress. (Guy et al., 2020; Wu et al., 2020b) Hydroxychloroquine was reported to significantly reduce the duration of therapy and decrease viral carriage. (Gautret et al., 2020) In COVID-19 cases treated with hydroxychloroquine, higher proportions of improvement and absorption of pneumonia were observed than in the untreated cases. (Zhaowei Chen et al., 2020) Replication of SARS-CoV-2 was inhibited by hydroxychloroquine *in vitro*. (Yao et al., 2020) Reduced clinical symptoms and recovery of lymphopenia were also observed in the hydroxychloroquine-treated patients. (Wei Tang et al., 2020) An emergency authorization for the use of hydroxychloroquine was issued by the USA FDA for the treatment of COVID-19. (Wu et al., 2020b) Nevertheless, there were controversies and even corrupted scientific behavior concerning hydroxychloroquine. (Almazrou et al., 2020; Annie et al., 2020; Carafoli, 2020; Prodromos and Rumschlag, 2020) Based on the

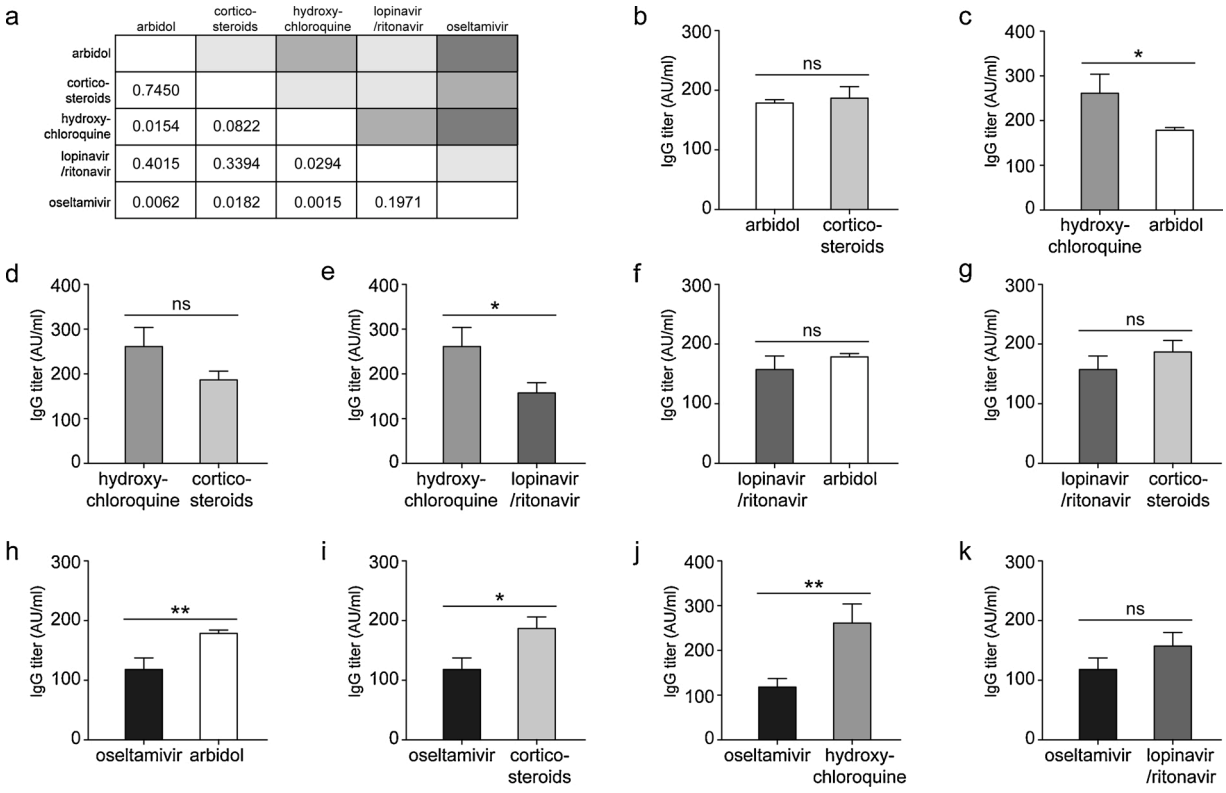

Fig. 3. Comparison of serological IgG level between different treatment groups. (a) Overall comparison of serological IgG level between different groups. *P* value was calculated and depicted. Grey color scale was used to describe the statistical significance. The darker the color, the greater the difference. Comparisons of serological IgG level were performed in each two groups: (b) the arbidol and corticosteroids groups, (c) the hydroxychloroquine and arbidol groups, (d) the hydroxychloroquine and corticosteroids groups, (e) the hydroxychloroquine and lopinavir/ritonavir groups, (f) the lopinavir/ritonavir and arbidol groups, (g) the lopinavir/ritonavir and corticosteroids groups, (h) the oseltamivir and arbidol groups, (i) the oseltamivir and corticosteroids groups, (j) the oseltamivir and hydroxychloroquine groups, and (k) the oseltamivir and lopinavir/ritonavir groups. *P* value was calculated using two-sided Student's *t*-test, and denoted as * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$, "ns" represents "not significant".

results from the first large-scale international trial on hydroxychloroquine, the WHO has immediately interrupted the trial and proclaimed its inefficiency, followed by national agencies cancelling the recommended use of hydroxychloroquine in the treatment of COVID-19. However, the paper was retracted owing to unsupported and fraudulent data, and the WHO resumed the trial. Recently, in the interim analysis of the SOLIDARITY trial, hydroxychloroquine was again denoted as inefficient. (Hongchao Pan et al., 2020) However, the inclusion criteria and the heterogeneity in the population might confound the results. (Hongchao Pan et al., 2020) Hydroxychloroquine could inhibit the interaction and thus the penetration of virus into the target cell and reduce the production of inflammatory cytokines, underlying its mechanisms of action against SARS-CoV-2. (Samaddar et al., 2020; Singh et al., 2020) In the present study, a promoting effect of hydroxychloroquine was observed. The shortened length of hospitalization and elevated levels of IgM and IgG further supported the use of hydroxychloroquine. However, limited by the small sample size, this encouraging conclusion should be interpreted cautiously and further evaluated in our future study, which will explore data from multiple designated hospitals in China.

The therapeutic effects of arbidol against SARS-CoV-2 are controversial. In a clinical pilot trial, arbidol could reduce viral load and decrease the mortality rate. (Wang et al., 2020c) However, in a prospective study, arbidol had inferior efficiency in clinical recovery and relief of symptoms. (Deng et al., 2020) In the 277 patients treated with arbidol, their hospitalization duration was longer than that of the patients treated with hydroxychloroquine, and their serological IgM and IgM titers were lower. Therefore, hydroxychloroquine may have superior effects compared to arbidol. The results of clinical trials on lopinavir/ritonavir are somewhat disappointing. In an open-label randomized controlled study, lopinavir/ritonavir monotherapy did not show a significant benefit over standard care. (Cao et al., 2020) By the observational endpoint, SARS-CoV-2 RNA was still detectable in 40.7 % of the patients in the lopinavir/ritonavir group. (Cao et al., 2020) Lopinavir/ritonavir or arbidol showed no improvement in outcomes compared to standard care, and the lopinavir/ritonavir group had an even higher deterioration rate of disease condition. (Yueping Li et al., 2020) Consistently, we could not find overt effects of lopinavir/ritonavir beyond the other four candidate drugs. Combination therapy of arbidol and lopinavir/ritonavir has shown an increased negative conversion rate of SARS-CoV-2 and improved chest CT results. (Deng et al., 2020) In view of these results, treatment regimens containing arbidol and lopinavir/ritonavir warrant further investigation. Since corticosteroids inhibit the immune response and pathogen clearance, corticosteroids were recommended not as the routine use in the treatment of COVID-19 except in patients with acute respiratory distress syndrome. (Alhazzani et al., 2020; Bhimraj et al., 2020) In a retrospective cohort study, corticosteroids treatment reduced the risk of death. (Wu et al., 2020a) In our analysis, corticosteroids were used in more serious patients, who were older, had a higher ICU administration rate, and had worse outcomes than the patients in the other four groups. However, we obtained no superior results. Balancing the benefits and adverse effects of corticosteroids requires additional investigations. (Wu et al., 2020b) Oseltamivir alone was reported as having no significant effect in fighting against COVID-19. (Wang et al., 2020a) This agent is not recommended in the management of the pandemic. (Sanders et al., 2020) The results herein indicated an even negative effect on IgG levels. Nevertheless, the oseltamivir group had a shorter length of hospital stay. From this viewpoint, oseltamivir may be used prudently in combination therapy

with hydroxychloroquine, the efficiency and safety of which should be evaluated in large-scale multicenter studies. Chloroquine can induce QTc interval prolongation, which would be exacerbated by oseltamivir. (Fihn et al., 2020) Hydroxychloroquine has a wider safety profile than chloroquine and the inhaled formulation provides a feasible approach. (Kavanagh et al., 2020; McKee et al., 2020; Singh et al., 2020)

In the current analysis, only patients treated with arbidol, corticosteroids, hydroxychloroquine, lopinavir/ritonavir, or oseltamivir monotherapy were included. However, in the COVID-19 crisis, many patients were treated with combination therapies. Patients receiving combination therapies were excluded to diminish the influences of sequential orders, dosage, and time, leaving a small sample size for further analysis. Owing to the small sample size, we were unable to identify a clear correlation between drug effects and treatment time. There is still no standardized regimen against COVID-19. The dosage and treatment time were mainly decided according to expert consensus or guidelines mostly empirically, and were adjusted according to the clinical reality. Therefore, the differences in drug schedules could confound the results. Another limitation is the retrospective nature of this study. The data analyzed were retrieved from archived medical records. After the relief of the COVID-19 pandemic in China, the designated hospitals were redefined, and we were unable to update the number of cases in this study owing to limited access. Furthermore, the insufficiency of medical supplies and the detection cost restrained dynamic monitoring of antibody levels in the general inpatients during the pandemic. Therefore, prospective, multicenter, large-scale studies containing more endpoints, such as the negative conversion duration of SARS-CoV-2 nucleic acids, are needed.

In summary, a comparison of drug effects against COVID-19 is instructive to fight against the COVID-19 pandemic. Drug repurposing is a promising way to combat SARS-CoV-2 infection. Hydroxychloroquine has the potential to treat COVID-19 efficiently. Oseltamivir can be prudently considered in combination therapy.

Funding

This work was supported by National Sci-Tech Support Projects [2018ZX10301402-002] and National Natural Science Foundation of China [81974405, 81572570]. The funding sources had no role in the design of the study; collection, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CRediT authorship contribution statement

Jiahong Tan: Methodology, Formal analysis, Writing - original draft, Visualization. **Yuan Yuan:** Methodology, Formal analysis, Writing - original draft, Visualization. **Cheng Xu:** Formal analysis, Visualization. **Chunyan Song:** Formal analysis, Visualization. **Dan Liu:** Formal analysis, Visualization, Funding acquisition. **Ding Ma:** Conceptualization, Supervision. **Qinglei Gao:** Conceptualization, Funding acquisition, Writing - review & editing, Supervision.

Declaration of Competing Interest

None.

Acknowledgements

We sincerely thank all individuals and communities involved in fighting against COVID-19.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.virusres.2020.198262.

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