The effect of Arbidol Hydrochloride on reducing mortality of Covid-19 patients: a retrospective study of real-world data from three hospitals in Wuhan

Qibin Liu[1], Xuemin Fang[1], Lu Tian[1], Ungil Chung[4], Xianxiang Chen[5], Ke Wang[6], Dan Li[7], Xiyong Dai[8], Qi Zhu[9], Feng Xu[10], Lei Shen[11], Bing Wang[12], Li Yao[13], Peng Peng[*]

[1] Wuhan Pulmonary Hospital, Wuhan Institute for Tuberculosis Control, No. 28 Baofeng Road, Qiaokou District, Wuhan City, Hubei Province, China; Liuqibin0221@163.com

[1] Graduate School of Health Innovation, Kanagawa University of Human Services, 2F Bldg.2-A, 3-25-10, Tonomachi Kawasaki-ku, Kawasaki City, Kanagawa 210-0821, Japan, mindy.fang@gmail.com

[1] Department of Biomedical Data Science, Stanford University, CA 94305, USA, lutian@stanford.edu

[4] Graduate School of Health Innovation, Kanagawa University of Human Services, 2F Bldg.2-A, 3-25-10, Tonomachi Kawasaki-ku, Kawasaki City, Kanagawa 210-0821, Japan, tei@tetrapod.t.u-tokyo.ac.jp

[5] Wuhan Pulmonary Hospital, Wuhan Institute for Tuberculosis Control, No. 28 Baofeng Road, Qiaokou District, Wuhan City, Hubei Province, China; 2272534937@qq.com

[6] Department of Pulmonary and Critical Care Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, 430030, Wuhan City, Hubei Province, China, Chinawangke13409@163.com

[7]Department of Pediatric Surgery, Union Hospital, Tongji Medical College, Huazhong

University of Science and Technology, 1277 Jiefang Avenue, 430022, Wuhan City, Hubei Province, China, D201478239@alumni.hust.edu.cn

[8] Wuhan Pulmonary Hospital, Wuhan Institute for Tuberculosis Control, No. 28 Baofeng Road, Qiaokou District, Wuhan City, Hubei Province, China, daixiyong71@126.com

[9]Wuhan Pulmonary Hospital, Wuhan Institute for Tuberculosis Control, No. 28 Baofeng Road, Qiaokou District, Wuhan City, Hubei Province, China, zhuqi197106@163.com

[10] Wuhan Pulmonary Hospital, Wuhan Institute for Tuberculosis Control, No. 28 Baofeng Road, Qiaokou District, Wuhan City, Hubei Province, China, victor_fsxq@163.com

[11]Wuhan Pulmonary Hospital, Wuhan Institute for Tuberculosis Control, No. 28 Baofeng Road, Qiaokou District, Wuhan City, Hubei Province, China, shen0811@aliyun.com

[12] Wuhan Pulmonary Hospital, Wuhan Institute for Tuberculosis Control, No. 28 Baofeng Road, Qiaokou District, Wuhan City, Hubei Province, China, 779238021@qq.com

[13]Wuhan Pulmonary Hospital, Wuhan Institute for Tuberculosis Control, No. 28 Baofeng Road, Qiaokou District, Wuhan City, Hubei Province, China, 354608920@qq.com

[*] Wuhan Pulmonary Hospital, Wuhan Institute for Tuberculosis Control, No. 28 Baofeng Road, Qiaokou District, Wuhan City, Hubei Province, China, pengpengwg@126.com;

Tel:+86-027-83605535; Fax: +86-027-83602499

BACKGROUND

The worldwide COVID-19 pandemic develops rapidly. There is a pressing need to find an effective therapy.

METHODS

We have assembled a cohort consisting 504 hospitalized COVID-19. Information of patients' characteristics and antiviral medication use during hospital stay is collected. The study objective is to evaluate the treatment efficacy of selected antiviral medications on mortality and lesion absorption based on chest CT scan.

RESULTS

The overall mortality rate was 15.67% in the cohort. Older age, lower SpO2 level, bigger lesion, early admission data, and the presence of pre-existing conditions were associated with higher mortality. After adjusting for sex, pre-existing condition, age, SpO2, lesion size, admission data, hospital, and anti-viral medications use, Arbidol and Oseltamivir use is associated with a reduction in mortality. The OR is 0.183 (95% CI, 0.075 to 0.446; p<0.001) for Arbidol and 0.220 (95% CI, 0.069 to 0.707; p=0.011) for Oseltamivir. Compared with patients taking neither Arbidol nor Oseltamivir, the OR is 0.253 (95% CI, 0.064 to 1.001; p=0.050) for patients taking Oseltamivir only; 0.190 (95% CI, 0.076 to 0.473; p<0.001) for patients taking Arbidol only; and 0.030 (95% CI, 0.003 to 0.310; p=0.003) for patients taking both, after adjusting for patients' characteristics and Lopinavir/Ritonavir use. Similarly, Arbidol is also associated with faster lesion absorption after adjusting for patient's characteristics as well as Oseltamivir and Lopinavir/Ritonavir use.

CONCLUSIONS

Arbidol is able to substantially associated with a reduction in mortality among hospitalized COVID-19 patients. The combination of Arbidol and Oselmativir may further associated with a reduction in mortality. There is no proven treatment benefit of Lopinavir/Ritonavir.

Introduction

Since December 2019, when first case of COVID-19 has been discovered in Wuhan, China[1], more than 1,000,000 infections and over 50,000 deaths have been reported[2-3]. Since the outbreak, researchers around the world have been actively searching for effective therapies, which are urgently needed to control the pandemic and is associated with a reduction in the mortality among infected. There were several case reports about recovery of COVID-19 patients after receiving certain treatment[4-5]. However, the lack of data remained an obstacle for reliable evaluation of the treatment effect of therapies attempted. There are several on-going clinical trials, whose completion, however, requires more time and resources with uncertain result[6-11].

On March 4, 2020, the Chinese National Health Commission issued the "New Coronary Virus Pneumonia Diagnosis and Treatment Program (Version 7)". The medications mentioned in the antiviral treatment program include Lopinavir/Ritonavir, Ribavirin, Chloroquine Phosphate, and Arbidol[12]. In addition, other antiviral drugs including Oseltamivir, Ganciclovir, Favipiravir and Remdesivir have also been used in clinical practice. Lopinavir/Ritonavir is commonly used in combination with other antiretroviral drugs to treat HIV infection[13-14]. Ribavirin is an antiviral drug mainly used for viral pneumonia and bronchitis caused by respiratory syncytial virus[15]. Chloroquine phosphate is originally used to treat chloroquine-sensitive falciparum,

vivax, and malaria[16]. Arbidol is mainly used to treat upper respiratory tract infections caused by influenza virus[17-18]. Oseltamivir and Favipiravir are also primarily used to treat influenza[19,20]. Ganciclovir is used for treating infections induced by cytomegalovirus, herpes simplex virus, and Epstein-Barr virus[21]. Remdesivir is a new drug, whose antiviral effect is unclear as relevant clinical trials are still ongoing[22].

When COVID-19 pandemic started, Wuhan Pulmonary Hospital (WPH) became one of the first COVID-19 designated hospitals and had received more than 700 COVID-19 patients by March 29, 2020. Wuhan Tongji Hospital and Wuhan Union Hospital are also designated hospitals treating a large number of COVID-19 patients. The clinical experience in battling COVID-19 in these three hospitals may guide the discovery of effective therapies of the disease. Our study objective is to evaluate the treatment effect of selected antiviral medications using real word data collected from these hospitals.

Methods

The study protocol was reviewed and approved by the Ethics committee of WPH (WPE 2020-12). Patient records and information were de-identified prior to the analysis.

STUDY POPULATION

We have assembled a cohort consisting 504 COVID-19 patients from three hospitals. For WPH, we started from all COVID-19 patients admitted between December 13, 2019 and March 21, 2020. We excluded patients with dubious diagnosis and those with a primary cause of death unrelated to COVID-19. After further exclusion of 119 patients, who have neither been discharged nor deceased until March 29, 2020, 373 patients from WPH were included. For Tongji Hospital, a randomly selected ward of 100 patients admitted between February 1, 2020 and February 5, 2002, was included. For Union Hospital, two randomly selected wards of 31 patients admitted between January 26, 2002 and February 24, 2002 were included. Therefore, all patients in the cohort have definitive outcomes, i.e., discharged or deceased. All infections are confirmed by virus nucleic acid test. Figure 1 demonstrates steps of constructing the cohort.

PATIENTS CHARACTERISCS, MEDICATION USE, AND ENDPOINTS

Treatment protocols in all three hospitals included Lopinavir/Ritonavir, and Arbidol. Some early protocols recommended Oseltamivir. With the development of the epidemic, Chloroquine Phosphate and Favipiravir had also been used for selected patients. The prescription of antiviral medications and their administration time for each patient were extracted from electronic medical records. In this study, we

specifically focus on the three most prescribed medications: Arbidol, Oselmativir, and Lopinavir/Ritonavir.

We collected data on patient characteristics having a known association with patients' outcome including age, sex, pre-existing conditions (eTable 1), SpO2 level at hospital admission, use of oxygen and ventilators during the hospital stay, and patient's first and the last available CT scan images.

The primary endpoint is in-hospital death, whose time is extracted from medical records. The secondary endpoint is the change in lesion size measured by CT scans. We measured the lesion size based on the first CT image after the patient's admission but before the initiation of the regular full-course antiviral treatment. We also measured the lesion size based on the last CT scan taken before patient's death or discharge, which is normally after completing the antiviral therapy cycle. To ensure the comparability of the two CT images, we selected the plane with the largest lesion in the first CT scan, and took the same plane in the second. The lesion in the selected plane was circled and quantified (eFigure 1) by ImageJ by NIH[23].

STATISTICAL ANALYSIS

Patient characteristics at baseline were summarized according to treatment and

hospital. Continuous and dichotomous variables were summarized by their mean (standard deviation (SD)), and count (proportion), respectively. We compared the mortality rate between patients who received the selected medication, and those who did not using Fisher's exact test. We then employed the logistic regression to estimate the odds ratio (OR) associated with the medication after adjusting for sex, pre-existing condition, medication use, hospital, and log-transformed age, SpO2 level, admission data as well as the lesion size from the initial CT scan. Missing covariates were imputed by the medians of the observed values. We also performed sensitivity analysis to evaluate the causal effect of the treatment using doubly robust method[24]. The analysis was restricted to patients whose estimated propensity scores were between 0.1 and 0.9[25]. We also repeated the logistic regression for patients in WPH only, where the potential sampling bias was the lowest. We checked the goodness of fit of the logistic regression with Hosmer-Lemeshow test[26]. In addition, we performed Cox regression analyses with time dependent covariates, setting value to 0 and 1 before and after the medication prescription, respectively, to account for the timing of medication use[27]. We also conducted linear regression analyses with the log-transformed ratio of lesion area at the second CT scan to that at the first as the outcome to study the effect of the antiviral medication on lesion absorption among surviving patients. A small value one was added to all lesions size to avoid log-transformation of zero. The two-sided statistical significance level was set at 0.05. All statistical analyses were conducted using R 3.3.1 (The R foundation for Statistical Computing).

Results

COHORT BASELINE CHARACTERITISCS

The cohort consists of 504 patients with confirmed COVID-19 infection from three hospitals: 373 patients from WPH, 100 patients from the Tongji Hospital, and 31 patients from the Union hospital. Table 1 summarized main treatments administrated during patient's hospital stay. Arbidol was prescribed to 257 patients (51.0%); Oseltamivir was prescribed to 66 patients (13.1%); and Lopinavir/Ritonavir was prescribed to 259 patients (51.4%). The median length of hospital stay was 14 days (Interquartile range (IQR): 9-22.25 days). Among 504 patients, 245 (48.6%) were females, and 262 (52.0%) had pre-existing conditions. The average age of the cohort was 59.5 (SD, 14.9) years old. The average SpO2 level at admission was 92.8% (9.3%). Table 2 summarized the patients characteristics by treatment and hospital. Patients receiving Arbidol had slightly higher SpO2 level and smaller lesion area. Patients receiving Oseltamivir were younger and less likely to have pre-existing conditions. In contrast, patients receiving Lopinavir/Ritonavir tended to have pre-existing conditions. Patients admitted to the hospital early were more likely to receive Oseltamivir and Lopinavir/Ritonavir.

THE EFFECT ON MORTALITY

The overall mortality rate was 15.67%. The mortality was 9.39% among females,

21.62% among males, 20.23% among patients with pre-existing conditions, 10.74% among patients without any pre-existing conditions, 17.96% among patients admitted into WPH, 12.00% among patients admitted into Tongji Hospital, and 0% among patients admitted into Union hospital. In this cohort, older age, lower SpO2 level at admission, bigger lesion, and early admission data were all associated with higher mortality (eFigure 2).

The mortality was 7.00% among patients who took Arbidol vs. 24.70% among patients who did not. The odds ratio (OR) was 0.230 (95% confidence interval (CI), 0.124 to 0.411) favoring Arbdiol. The mortality was 12.12% among patients who took Oseltamivir, vs. 16.21% among patients who did not. The OR was 0.713 (95% CI, 0.282 to 1.589). The mortality was 14.29% among patients who took Lopinavir/Ritonavir, vs. 17.14% among patients who did not. The OR was 0.806 (95% CI, 0.483 to 1.341). After adjusting for sex, pre-existing condition, log(age), log(SpO2), log(lesion size), log(admission data) and hospital, all three antiviral medications were individually associated with a reduction in mortality: the adjusted OR was 0.169 (95% CI, 0.071 to 0.398) for Arbidol, 0.212 (95% CI, 0.072 to 0.623) for Oseltamivir, and 0.363 (95% CI, 0.165 to 0.795) for Lopinavir/Ritonavir. After further adjustment of antiviral medications use, the protective effect of Arbidol and Oseltamivir remained statistically significant: the adjusted OR was 0.183 (95% CI, 0.075 to 0.446; $p<0.001$) for Arbidol and 0.220 (95% CI, 0.069 to 0.707; $P=0.011$) for Oseltamivir (Figure 2). The Hosmer-Lemeshow test for this regression model suggested satisfactory goodness

of fit (P=0.427). Furthermore, compared with patients taking neither Arbidol nor Oseltamivir, the OR was 0.253 (95% CI, 0.064 to 1.001; P=0.050) for patients taking Oseltamivir only; 0.190 (95% CI, 0.076 to 0.473; p<0.001) for patients taking Arbidol only; and 0.030 (95% CI, 0.003 to 0.310; P=0.003) for patients taking both, after adjusting for patients' characteristics and Lopinavir/Ritonavir use.

THE EFFECT ON LESION SIZE

There were 326 survivors with two available CT scans. The average reduction in lesion size between two scans was 46.43% (29.00%) among 209 patients taking Arbidol and 36.80% (SD: 24.95%) among 117 patients who did not. The average reductions among 55 patients taking Oseltamivir was less than that among 271 patients not taking (41.18% vs 43.34%). The reduction among 186 patients taking Lopinavir/Ritonavir was also less than 140 patients not taking (37.26% vs. 50.56%). After adjusting for patients' characteristics and antiviral medication use, the ratio of the lesion size after the treatment vs that before among patients taking Arbidol was 85.20% (95% CI, 74.47% to 97.48%; P=0.0203) of that among patients not taking Arbidol, suggesting faster lesion absorption. Figure 3 summarized the analysis results for all three medications. eFigure 3 shows the distribution of the lesion absorption rates by medication.

SENSITIVITY ANALYSIS

DOUBLY ROBUST ADJUSTMENT

Of the 373 patients from WPH, 200 patients took neither Arbidol nor Oseltamivir, and 127 patients took only Arbidol. In order to study the causal effect of Arbidol, we compared the mortality between these two groups, after excluding 22 patients with an estimated propensity score (based on sex, pre-existing condition, log(age), log(SpO2), log(baseline lesion size), log(admission data) and Lopinavir/Ritonavir use) greater than 0.9 or less than 0.1. The doubly adjusted mortality estimate was 18.06% (95% CI, 12.88% to 23.44%) for patients taking neither, and 7.03% (95% CI, 2.99% to 11.42%) for patients taking Arbidol only. Compared with patients taking neither, the OR was 0.343 (95% CI, 0.142 to 0.638; P<0.001) favoring Arbidol. eTable 2 summarized the patients' characteristics by treatment before and after propensity score reweighting.

SUBGROUP ANALYSIS IN WPH

Of the 373 patients in WPH, the mortality was 7.09% among patients taking Arbidol vs. 24.57% among those not (OR=0.234, 95% CI, 0.103 to 0.481, P<0.001). After adjusting for sex, pre-existing condition, log(age), log(SpO2), log(lesion area), log(admission data), and antiviral medication use, Arbidol was significantly associated with a reduction in mortality (OR, 0.193; 95% CI, 0.071 to 0.520, P=0.001). The effect of Oseltamivir was marginally significant (OR, 0.326; 95% CI, 0.090 to 1.177; P=0.087). eFigure 4 summarized detailed results. Compared with patients taking neither Arbidol nor Oseltamivir, the OR was 0.268 (95% CI, 0.064 to 1.124) for

Oseltamivir only group; 0.173 (95% CI, 0.060 to 0.499, P=0.001) for Arbidol only group; and 0.114 (95% CI, 0.011 to 1.156) for Arbidol and Oseltamivir combo group.

SURVIVAL ANALYSIS

Among patients taking Arbidol, the median prescription time was 1.5 (rang, 0.5-31.5) days after admission. For Oseltamivir and Lopinavir/Ritonavir, the median prescription time was 0.50 (range, 0.5-25.5) and 0.50 (range, 0.5-32.5) days after admission, respectively. After adjusting for baseline characteristics and antiviral medication use, the hazard ratio was 0.350 (95% CI, 0.177 to 0.689; P=0.002) for Arbidol, 0.571 (95% CI, 0.269 to 1.211) for Oseltamivir, and 0.720 (95% CI, 0.426 to 1.218) for Lopinavir/Ritonavir based on Cox regression stratified by hospitals. Compared with patients taking neither Arbidol nor Oseltamivir, the hazard ratio was 0.639 (95% CI, 0.283 to 1.442) for Oseltamivir only group; 0.365 (95% CI, 0.183 to 0.727; P=0.004) for Arbidol only group; and 0.122 (95% CI, 0.016 to 0.956; P=0.045) for Arbidol and Oseltamivir combo group. eFigures 5-7 and eFigure 8 showed the cumulative mortality rate curves by medication use and detailed regression analysis results, respectively.

Discussion

In all analyses, the treatment effect of Arbidol on reducing mortality among hospitalized COVID-19 patients is strong and robust. The combined use of Arbidol and Oseltamivir appears to be able to further is associated with a reduction in the mortality. In

addition, patients taking Arbidol shows faster lesion absorption, which is consistent with its effect on mortality. On the other hand, the benefit of Lopinavir/Ritonavir is inconclusive, which is in consistent with the finding of Cao et al. (2020), where Lopinavir/Ritonavir has associated with a reduction in the 28-day mortality from 25.0% to 19.2% in a randomized clinical trial, but fails to reach the statistical significance threshold[4]. Recently, Xu et al, (2020) reported that the virologic conversion rate in 49 patients taking Arbidol was significantly higher than that in 62 patients only receiving standard care (59.2% vs 40.3%, P=0.048). In the same study, the patients taking Arbidol also had a higher chance of achieving lesion area absorption on CT images (55.1% vs 32.2%)[27]. Despite limited sample sizes, their results further corroborate our findings. Arbidol's duo role in inhibiting the fusion between the viral envelope and target host cell membrane and in anti-inflammation may be responsible for its efficacy[28, 29].

Oseltamivir is normally prescribed for treating influenza and has no known effect on COVID-19 patients. However, influenza is clinically similar to COVID-19 and some patients have been infected by both COVID-19 and common Influenza[30], which may exacerbate their clinical conditions. It is possible that a combo therapy including Oseltamivir can help this subgroup of patients due to the effectiveness of Oseltamivir in treating severe illness caused by Influenza.

There are several important limitations in the current study. The study is not a

randomized clinical trial, and therefore the estimated treatment benefit of Arbidol and Oseltamivir may be due to confounding effect. We have collected the information on known confounders including age, comorbidities, admission data, and disease severity measured through SpO2 and CT scan. However, there is always a risk of unmeasured confounders, which can explain the observed treatment effect. On the other hand, given the size of the observed benefit, the unmeasured confounding effect needs to be very strong to completely account for the estimated benefit. Secondly, we didn't account for the effect of important supporting treatment such as oxygen and ventilator use. Their availability and deployment may affect the estimated treatment effect. Thirdly, although the cohort size is not small, the patients from Tongji and Union hospitals are not necessarily the most representative samples of patients admitted into these hospitals. For example, ICU patients in these two hospitals are not included. We have also excluded surviving patients not discharged from WPH, and consequently, the observed mortality rate among patients from WPH in this cohort is substantially higher than that among all patients admitted into WPH. These sampling biases may affect the generalizability of our findings. Furthermore, there are only 33 patients taking both Arbidol and Oseltamivir in the entire cohort, which limits the reliability of the estimated treatment benefit associated with the combination therapy. On the other hand, despite limited sample size and selective sampling, all identified risk factors in the current study are consistent with the literature [31], which indirectly supports the validity of our findings on treatment efficacy. The association between admission data and mortality can also be explained by increasing medical resource. Lastly regarding the

adverse events, a few cases of nausea were observed in patients who have received Arbidol; Loss of appetite were observed among patients who have received Oseltamivir; Diarrhea, nausea, vomiting, loss of appetite, and worsened sleep quality were observed in patients who have received Lopinavir/Ritonavir. However, since a large proportion of the patients have received multiple medications, due to the complexity of the nature of the adverse events, the study team did not summarize these data in this report. On the other hand, Arbidiol and Oseltamivir have been used to treat influenza patients for many years and the severe adverse event associated with the medicine has been rare [17,19].

Conclusion: in this cohort of 504 COVID-19 patients from three hospitals, Arbidol alone and in combination with Oseltamivir are associated with drastically associated with a reduction in mortality after accounting for all observed confounders.

Table 1: Administrated treatments for patients in three hospitals

Medication\ Hospital	WPH n=373	Tongji n=100	Union n=31	Total n=504
Arbidol	141 (37.8%)	94 (94.0%)	22 (71.0%)	257 (51.0%)
Oseltamivir	46 (12.3%)	19 (19.0%)	1 (3.2%)	66 (13.1%)
Lopinavir/Ritonavir	245 (65.7%)	4 (4.0%)	10 (32.3%)	259 (51.4%)
Chloroquine	4 (1.1%)	0 (0.0%)	0 (0.0%)	4 (0.8%)
Hydroxycholoroquine	3 (0.8%)	0 (0.0%)	0 (0.0%)	3 (0.6%)
Favipiravir	4 (1.1%)	0 (0.0%)	0 (0.0%)	4 (0.8%)
Ganciclovir	28 (7.5%)	0 (0.0%)	2 (6.5%)	30 (6.0%)
Glucocorticoid	151 (40.5%)	73 (73.0%)	6 (19.4%)	230 (45.6%)
Immunoglobin	117 (31.4%)	25 (25.0%)	10 (32.3%)	152 (30.2%)
Albumin	71 (19.0%)	15 (15.0%)	2 (6.5%)	88 (17.5%)
Oxygen	318 (85.3%)	86 (86.0%)	23 (74.2%)	427 (84.7%)
Ventilation	43 (11.5%)	12 (12.0%)	0 (0%)	55 (10.9%)

Table 2. Distributions of Baseline Characteristics by Medication and Hospital

	WPH		Tongji		Union		Total	
	Arbidol							
	Yes n=141	No n=232	Yes n=94	No n=6	Yes n=22	No n=9	Yes n=257	No n=247
Age (year)	61.3 (14.2)[(1)]	60.3 (15.0)	55.8 (14.6)	68.5 (9.6)	58.2 (17.3)	46.4 (15.3)	59.1 (14.8)	60.0 (15.1)
Female	72 (51.1%)	112 (48.3%)	41 (43.6%)	3 (50.0%)	12 (54.5%)	5 (55.6%)	125 (48.6%)	120 (48.6%)
Pre-existing conditions	90 (63.8%)	119 (51.3%)	33 (35.1%)	5 (83.3%)	11 (50.0%)	4 (44.4%)	134 (52.1%)	128 (51.8%)
SpO2 level (%)	93.6 (4.3)	91.7 (12.2)	93.9 (6.4)	81.3 (14.9)	95.8 (1.4)	96.8 (1.1)	93.9 (5.0)	91.6 (12.1)
Lesion Size (cm^2)	56.1 (43.4)	65.5 (48.4)	46.8 (31.2)	44.6 (19.7)	55.4 (38.9)	50.8 (42.6)	52.7 (39.1)	64.6 (47.9)
Admission Data[(2)] (day)	65.0 (13.4)	61.2 (22.0)	52.8 (1.4)	52.5 (1.4)	55.5 (7.3)	55.4 (5.5)	59.7 (11.7)	60.8 (21.4)
	Oseltamivir							
	Yes n=46	No n=327	Yes n=19	No n=81	Yes n=1	No n=30	Yes n=66	No n=438
Age (year)	59.1 (13.5)	60.9 (14.8)	52.1 (12.8)	57.7 (14.9)	66.0	54.4 (17.5)	57.2 (13.6)	59.9 (15.1)
Female	24 (52.2%)	160 (48.9%)	9 (47.4%)	35 (43.2%)	1 (100%)	16 (53.3%)	34 (51.5%)	211 (48.2%)
Pre-existing Conditions	27 (58.7%)	182 (55.7%)	4 (21.1%)	34 (42.0%)	1 (100%)	14 (46.7%)	32 (48.5%)	230 (52.5%)
SpO2 level (%)	92.8 (6.4)	92.4 (10.4)	92.6 (7.7)	93.3 (7.7)	94.0	96.2 (1.3)	92.8 (6.7)	92.8 (9.6)
Lesion Size (cm^2)	67.8 (46.1)	60.3 (46.5)	47.1 (39.5)	46.7 (28.5)	43.0	54.5 (39.8)	61.5 (44.6)	57.2 (43.4)
Admission Data (day)	42.2 (10.1)	65.5 (18.5)	53.2 (1.2)	52.6 (1.4)	63.0	55.2 (6.7)	45.7 (10.0)	62.4 (16.9)
	Lopinavir/Ritonavir							
	Yes n=245	No n=128	Yes n=4	No n=96	Yes n=10	No n=21	Yes n=259	No N=245
Age (year)	60.3 (13.4)	61.4 (16.9)	39.2 (16.3)	57.3 (14.2)	53.5 (12.4)	55.4 (19.5)	59.7 (13.6)	59.3 (16.2)
Female	122	62	2	42	6	11	130	115

	(49.8%)	(48.4%)	(50.0%)	(43.8%)	(60.0%)	(52.4%)	(50.2%)	(46.9%)
Pre-existing Conditions	145 (59.2%)	64 (50.0%)	1 (25.0%)	37 (38.5%)	5 (50.0%)	10 (47.6%)	151 (58.3%)	111 (45.3%)
SpO2 level (%)	92.5 (8.5)	92.2 (12.4)	95.0 (4.1)	93.1 (7.8)	96.9 (0.9)	95.7 (1.4)	92.7 (8.3)	92.9 (10.2)
Lesion Size (cm^2)	61.6 (47.2)	61.0 (44.9)	22.6 (17.3)	48.0 (31.0)	44.4 (30.8)	59.0 (42.6)	60.2 (46.6)	55.1 (39.5)
Admission Data (day)	58.1 (15.4)	71.4 (22.7)	53.0 (1.6)	52.7 (1.4)	52.8 (5.0)	56.7 (7.2)	57.8 (15.0)	62.8 (18.8)

(1): SD; (2): December 13, 2019, when the first patient was admitted, is set as Day 1 for admission Data

Figure legends

Figure 1: Patient inclusion and exclusion criteria

Figure 2: The estimated OR and associated 95% CI for Arbidol, Oseltamivir and Lopinavir/Ritonavir. Model 1: adjusting for sex, pre-existing condition, log(age), log(SpO2), hospital, log(lesion size) and log(admission data); Model 2: adjusting for confounders in Model 1 and medication use (Arbidol, Oseltamivir, and Lopinavir/Ritonavir).

Figure 3: The estimated effect on relative change in lesion size and associated 95% CI for Arbidol, Oseltamivir and Lopinavir/Ritonavir. An effect less than 1 suggests that more relative reduction in lesion size is associated with the medicine of interest. Model 1: adjusting for sex, pre-existing condition, hospital, log(age), log(SpO2), log(lesion size) and log(admission data); Model 2: adjusting for confounders in Model 1 and medication use (Arbidol, Oseltamivir, and Lopinavir/Ritonavir).

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