

The effectiveness of antiviral treatment in severe COVID-19 patients in Wuhan: a retrospective cohort study

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Research

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Abstract

Background Since the outbreak of COVID-19, the application of appropriate treatment strategy for COVID-19 patients, notably for the severe patients, was a huge challenge in case management. Therefore, we aimed to evaluate the effectiveness of antiviral treatment in severe COVID-19 patients.

Methods A retrospective cohort study was conducted from January 8, 2020 to March 9, 2020 in four designated hospitals of COVID-19 in Wuhan, China. 138 severe COVID-19 patients with above 18 years were included in this study. 109 patients receiving the antiviral treatment were selected in antiviral group. The remaining 29 patients were in control group. The primary outcome of the study was in-hospital death and length of hospitalization. Secondary outcomes included ICU admission, length of stays in ICU, use of mechanical ventilation, length of mechanical ventilation, and the development of complications. Univariate analysis and Kaplan-Meier curves were used to examine the association between antiviral treatment and the clinical outcomes of the COVID-19 patients.

Results 48 (44.0%) and 15 (51.7%) deaths were occurred in antiviral and control groups, respectively. Antiviral treatment was not associated with the rate of fatal outcome in COVID-19 patients ($P > 0.05$). Among the survival patients, the median length of hospitalization was 11.0 days (IQR: 6.5–18.0) and 16.0 days (IQR: 8.5–26.0) in antiviral and control groups, respectively. No significant association was identified between the antiviral treatment and the length of hospitalization in survival patients ($P > 0.05$). Moreover, the antiviral treatment was not statistically associated with ICU admission, mechanical ventilation and length of mechanical ventilation ($P > 0.05$, respectively). However, the length of ICU stays in deaths was different both groups ($P < 0.05$). The median length of ICU stays in deaths was 7.0 days (IQR: 3.0–14.3) and 15.5 days (IQR: 8.3–21.8) in antiviral and control groups, respectively. The occurrence of majority of complications were similar both groups. Sepsis was the single complication in which the occurrence rates were statistically different between the antiviral group and control group (40.4% vs 13.8%, $P < 0.01$).

Conclusion No benefit of antiviral treatment in severe COVID-19 patients was observed in our study. Clinical physicians should cautiously prescribe the antiviral drugs in severe COVID-19 patients.

Introduction

Pandemic of coronavirus disease 2019 (COVID-19) led to 4.7 million cases and 0.3 million deaths in five months [1]. COVID-19 was caused by an emerging infectious pathogen that named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. The treatment strategy of an emerging infectious disease was a huge challenge for clinical practitioners because of missing the key knowledges about the diseases. Although most of COVID-19 patients presented only mild symptoms, such as fever, cough, expectoration, chest distress, etc [3]. However, a part of COVID-19 patients developed the severe complications, even death [4]. Therefore, it is critical to improve the case management of severe cases, in order to reduce the mortality of COVID-19. However, no specific therapeutic agents for COVID-19 was provided. As SARS-CoV-2 belongs to the Coronavirus family, clinical physicians tended to use antiviral drugs (e.g., abidor, ribavirin, oseltamivir, etc.) in the COVID-19 treatment. Recently, two randomized clinical trials (RCT) showed that the use of lopinavir-ritonavir and chloroquine diphosphate could not improve the clinical course of COVID-19 patients [5, 6]. Nevertheless, the effectiveness of antiviral treatment in severe patients of COVID-19 were still unclear. Therefore, we conducted a retrospective cohort study to evaluate the effectiveness of the antiviral treatment in severe patients of COVID-19.

Methods

Study setting

This retrospective cohort study was conducted in four following designed hospitals of COVID-19 in Wuhan, China: Zhongnan Hospital of Wuhan University, Wuhan Third Hospital, Union Jiangbei Hospital and the First People's Hospital of Jiangxia District. This study was approved by the Medical Ethics Committee of the above four hospitals.

Study participants

138 severe COVID-19 patients aged above 18 years and admitted in the study hospitals between January 8, 2020 and March 9, 2020 were enrolled. The SARS-CoV-2 laboratory test assays were based on the recommendation of WHO [7]. According with the guidelines of the National Health Commission (NHC) of China [8], a severe case was defined as the case who corresponds to one of the following criteria: (1) respiratory distress or respiratory rate ≥ 30 breaths per minute; (2) oxygen saturation on room air at rest $\leq 93\%$; or (3) partial pressure of oxygen in arterial blood or fraction of inspired oxygen ≤ 300 mmHg (1 mmHg = 0.133 kPa). A critical case was defined as the case who corresponds to one of the following criteria: (1) respiratory failure occurs and mechanical ventilation is required; (2) shock; or (3) patients

with other organ dysfunction needing intensive care unit (ICU) admission. In our study, all the severe and critical patients were grouped and labeled severe patients.

Exposure

All the patients receiving any antiviral treatment, including ribavirin, oseltamivir, abidor, interferon, and Kaletra (i.e. lopinavir/ritonavir), were selected in antiviral group. The patients receiving the treatment other than antiviral were selected in control group. Among the 138 severe patients of COVID-19, 109 (79.0%) were classified in antiviral group and 29 (21.0%) in control group. The daily doses of ribavirin, oseltamivir, abidor, interferon, and Kaletra were 0.8 g, 150 mg, 400mg, 8 million IU, and 800 mg, respectively. The cumulative duration of antiviral treatment was defined as the period between the first prescription date and the end of the final prescription.

Outcomes

The primary outcome was defined as the in-hospital death and duration of hospitalization. The secondary outcomes included the ICU admission, length of stays in ICU, use of mechanical ventilation, length of mechanical ventilation, and the development of complications. The complications of COVID-19 patients consisted of Acute respiratory distress syndrome (ARDS), sepsis, septic shock, acute kidney injury (AKI), acute cardiac injury, and disseminated intravascular coagulation (DIC). ARDS was determined according to the Berlin Definition [9]. Sepsis and septic shock were diagnosed according to the 2016 Third International Consensus Definition for Sepsis and Septic Shock [10]. AKI was diagnosed according to the KDIGO clinical practice guidelines [11], and acute cardiac injury was diagnosed by increased serum cardiac biomarkers. DIC was defined according to the guidelines of the Scientific Subcommittee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis [12].

Data collection and covariates

The demographic and clinical data of patients, and the prescription and dispensing of drugs were extracted from the electric medical records. The covariates of analysis were defined as following: patients' basic characteristics (e.g. age, sex, body mass index (BMI), and smoking), co-morbidities, surgery history, clinical signs and symptoms (e.g. fever, cough, sputum production, chest distress, etc.), ventilation mode at admission, vital signs and laboratory findings, and the treatments other than antiviral (e.g. antibiotics, glucocorticoids, vasoactive drugs, high-flow oxygen therapy, etc.).

Statistical Analysis

The descriptive data were expressed as mean \pm standard deviation (SD) or median with interquartile range (IQR) or range for the continuous variables. The number and percentage were used for describing the categorical variables. The statistical comparison between antiviral and control groups used *t* test for normally distributed data, Mann-Whitney test for non-normally distributed or graded variables, and chi-square (χ^2) test or Fisher's exact test for discrete variables. Kaplan-Meier analysis was applied for survival time analysis during hospitalization. The log-rank test was used to compare the length of hospitalization in survival patients and deaths. The survival analysis was stratified by the combined treatments in survival patients and deaths. All analyses were performed with the use of R software (version 3.6.3, R Foundation for Statistical Computing). Two-sided *P* values of less than 0.05 were considered to indicate statistical significance.

Results

General characteristics

In total, 138 severe patients were enrolled in our study. 109 (79.0%) patients were in antiviral group, and 29 (21.0%) in control group. The mean age of the 138 patients was 65.4 years old (SD: \pm 12.6), and 90 (65.2%) patients were men (Table 1). Only 8 (5.8%) cases were smokers. 86 (63.3%) cases had coexisting disorders, including hypertension, diabetes, coronary heart disease, and renal insufficiency, chronic lung disease, cerebrovascular diseases, and malignant tumor (Table 1). 40 (29.0%) with a single co-morbidity and 46 (33.3%) with two or more co-morbidities. The most common symptoms at illness onset were fever, cough or expectoration, chest distress or dyspnea, fatigue, and breathlessness or wheezing (Table 1). The general characteristics were similar between the patients in antiviral group and that in control group. The vital signs and laboratory findings were also compared between the antiviral group and control group (Additional file 1: Table S1). No statistical differences in vital signs and most of laboratory findings were identified both groups.

Treatments

Among the 109 patients receiving the antiviral treatment, five different antiviral drugs were used. Ribavirin (36.2%) and oseltamivir (32.6%) were the mostly used antiviral drugs, followed by abidor (16.7%), interferon (11.6%), and Kaletra (5.1%) (Table 2). The duration of the antiviral

treatment varied with the specific antiviral drugs, ranging from 3 days for Kaletra to 9 days for interferon. Most of the patients (85, 78.0%) in antiviral group received a single antiviral drug, and 24 (22.0%) received a combined antiviral therapy.

For the 29 patients in control group, the application of antibiotics was the main drug treatment (93.1%), followed by glucocorticoids (62.1%) and vasoactive drugs (34.5%). However, the patients in antiviral group also received antibiotics (97.2%), glucocorticoids (73.4%) and vasoactive drugs (30.4%) (Table 3). In these drugs treatments, only duration of glucocorticoids therapy has a significant difference between antiviral group and control group ($P < 0.05$). The median duration of glucocorticoids therapy in antiviral group was 4.0 days (IQR: 2.0-9.0), and 8.0 days (IQR: 3.8-15.3) in control group. Moreover, the frequency of use of high-flow oxygen in antiviral group was significantly lower than that in control group (28.4% vs 48.3%, $P < 0.05$). The utilization rate of non-invasive ventilation in antiviral group was also significantly lower comparing with the control group (28.4% vs 51.7%, $P < 0.05$). However, the utilization rates of invasive mechanical ventilation were similar both groups (51.4% vs 58.6%, $P > 0.05$). Moreover, 12 of 138 patients (8.7%) received prone position ventilation, nine (9/109, 8.3%) in antiviral group and three (3/29, 10.3%) in control group. 7 of 138 (5.1%) patients received continuous renal replacement therapy (CRRT), four (4/109, 3.7%) in antiviral group and three (3/29, 10.3%) in control group.

Outcomes and complications

In total, 63 (45.7%) patients died during hospitalization and 75 (54.3%) were discharged. The case-fatality rates were similar between the antiviral group and control group (44.0% vs 51.7%, $P > 0.05$, Table 4). Moreover, the length of hospitalization of severe patients in antiviral group (median: 11.0, IQR: 6.5-18.0) was similar compared with that in control group (median: 16, IQR: 8.5-26.0, $P > 0.05$, Table 4 and Fig. 1A). For the deaths, the in-hospital survival time did not significantly differ between these two groups (Fig. 1B). For the survival patients, the length of hospitalization also had not statistical difference between these two groups (Fig. 1C). In addition, the survival analyses stratified by the combined treatments showed no significant difference on survival time or hospitalization length between the antiviral group and control group (Additional file 1: Fig. S1-S3).

In total, 131 patients (94.9%) were admitted to the ICU, 106 (97.2%) from antiviral group and 25 (86.2%) from control group (Table 4). 56 (51.4%) and 17 (58.6%) patients were received mechanical ventilation in antiviral and control groups, respectively. The rates of ICU admission, mechanical ventilation, and the length of mechanical ventilation did not differ between these two groups ($P > 0.05$, respectively, Table 4 and Fig. 3). However, length of ICU stays of severe patients in antiviral group was significantly shorter than that in control group (median [IQR], 9 [3-14] vs 15 [7-23.5], $P = 0.01$, Fig. 2A). The length of ICU stays of deaths was shorter in antiviral group (median: 7.0, IQR: 3.0-14.3) than that in control group (median: 15.5, IQR: 8.3-21.8, $P < 0.05$, Fig. 2B). The length of ICU stays of survival patients were similar both groups (Fig. 2C).

In total, 120 (87.0%) cases developed the complication, 99 (90.8%) were in antiviral group and 21 (72.4%) in control group. Respiratory failure (76.1%) was the most common complication, followed by ARDS (50.7%), sepsis (34.8%), acute cardiac injury (27.5%), acute liver injury (26.1%), acute kidney injury (22.5%), septic shock (17.4%), DIC (8.0%), arrhythmia (7.2%), gastrointestinal bleeding (5.1%) and acute cerebrovascular disease (3.6%) (Table 4). Only the sepsis incidence was significantly higher in antiviral group compared with the control group (40.4% vs 13.8%, $P < 0.01$). The incidence of the remaining complications was similar both groups (Table 4).

Discussion

The results of this study suggested that the antiviral treatment was not associated with clinical improvement or reduction of mortality in severe patients of COVID-19. Although antiviral therapy seemed to reduce the length of stay in ICU for the patients of COVID-19, this length was only shortened in the deaths with antiviral treatment. In addition, antiviral treatment might increase the risk of developing sepsis in severe patients.

The effectiveness of antiviral treatment for COVID-19 is still controversial. Many researchers consider that ribavirin, remdesivir, lopinavir, emetine, and homoharringtonine have shown efficacy to inhibit SARS-CoV-2 or other coronavirus replication in vitro and combinational therapy may help to reduce the effective concentration of SARS-CoV-2 [13–16]. The molecular docking study has shown that the effectiveness of ribavirin, remdesivir, sofosbuvir, galidesivir and tenofovir as potent drugs for treating SARS-CoV-2 infection [17]. Another study proposed a combination of lopinavir, oseltamivir and ritonavir for controlling the virulence to a great extent in COVID-19 patients within 48 hours, and the combination of these three drugs had a better binding energy than single use [18]. Results of molecular modelling tools suggested that ribavirin, telbivudine, vitamin B12 and nicotinamide can be combined and used for COVID-19 treatment [19]. Atazanavir, remdesivir, efavirenz, ritonavir, dolutegravir, lopinavir, darunavir and Kaletra showed an inhibitory effect against the SARS-CoV-2 in the drug-target interaction deep learning models, which may be used for the treatment of SARS-CoV-2 infection [20]. Interferon, as broad-spectrum antiviral biologicals, may account for a safe and easy to upscale treatment against COVID-19 in the early stages of infection [21, 22], because exogenous infection may stimulate antiviral immunity against SARS-CoV-2 [23]. And both therapeutic regimens of interferon- α +

lopinavir/ritonavir and interferon- α + lopinavir/ritonavir + ribavirin might be beneficial for treatment of COVID-19 in case series analysis [24]. One case report showed that late initiation of remdesivir might be effective in treating SARS-CoV-2 infection [25]. Another case report publication suggested that antiviral treatment including lopinavir/ritonavir, arbidol, and Shufeng Jiedu Capsule (i.e. a traditional Chinese medicine) could improve clinical symptoms in severe COVID-19 patients [26]. One case series in Chongqing of China demonstrated Kaletra and traditional Chinese medicine played an important role in the treatment of the viral pneumonia [27]. As such, many clinical physicians suggest that antiviral therapy is vital to reduce mortality in severe patients of COVID-19 [28]. However, our study observed no beneficial effects of antiviral drugs in severe COVID-19 patients.

However, the clinical effects of antiviral treatment are debatable to date. One study showed that oseltamivir has even no documented in vitro activity against SARSCoV-2 [29] and no benefit of oseltamivir treatment was observed in a single-center case series [30]. Although several publications have demonstrated with the potential efficacy to COVID-19 in humans, mostly through vitro experiments, pharmacological studies, case reports or case series analysis with small sample sizes. Therefore, RCT must be undertaken to further evaluate the efficacy of antiviral treatment. Recently, the World Health Organization (WHO) launched a multinational randomized trial, which study the effect of drugs that have been identified as promising based on in-vitro data and the early clinical experience with COVID-19, including remdesivir, lopinavir + ritonavir, lopinavir + ritonavir + interferon, and chloroquine/hydroxychloroquine [31]. One review also found 24 clinical trials that have already started with the repositioning of more than 20 medicines for COVID-19 treatment, such as human immunoglobulin, interferons, chloroquine, hydroxychloroquine, arbidol, remdesivir, favipiravir, lopinavir, ritonavir, oseltamivir, methylprednisolone, bevacizumab, and traditional Chinese medicines [32]. In addition, a recent RCT has showed that antiviral drug (lopinavir–ritonavir) did not accelerate clinical improvement, reduce mortality, or diminish throat viral RNA detectability in patients with severe COVID-19 cases [5]. The higher chloroquine diphosphate dosage should not be recommended for critically COVID-19 patients in another RCT [6]. Similar findings have been identified in our cohort study. Our study showed that the risk of mortality, clinical course of severe COVID-19 patients did not improve with the use of antiviral drugs.

Sepsis was one of the common complications of COVID-19. The incidence of sepsis was higher in the antiviral group in our study. Although the bacterial infections are usually regarded as a leading cause of sepsis, one study suggested that viral infection may also cause sepsis syndrome [3]. In severe COVID-19 patients, alveolar macrophages or epithelial cells could produce various proinflammatory cytokines and chemokines in response to the infection of SARS-CoV-2. Virus infection might lead to more macrophage infiltration and the immune pathogenesis caused by the systemic cytokine storm [33]. And the microcirculation dysfunctions lead to viral sepsis. But further research is necessary to investigate the pathogenesis of sepsis in COVID-19. In our study, we found that more than 40% of patients had leucocytes over 9.5×10^9 per L, neutrophils over 6.3×10^9 per L or procalcitonin over 0.5 ng/mL in all patients on admission. These findings revealed the bacterial infection in COVID-19 patients, but it is not persuasive to explain the high incidence of sepsis in COVID-19 patients receiving antiviral treatment. It may be due to disturbances of balance between virus-bacteria interactions by antiviral treatment [34], and virus clearance indirectly assist bacterial infection to induce a cytokine storm syndrome.

Our retrospective cohort study has some limitations. Firstly, the reliance on antiviral drugs use history to determine antiviral treatment exposures, while the assignment of the antiviral treatment was subject to the situation and environment of the hospital. The full extent of exposures may not have been captured. Secondly, our study only included the severe patients of COVID-19. The effectiveness of antiviral treatment in mild patients of COVID-19 cannot be analyzed in our study. Thirdly, the multivariate analysis was not carried out. The baseline characteristics of the severe COVID-19 patients were similar between antiviral group and control group. The confounding effect of other treatments was controlled by stratified analysis. Therefore, our analysis accounted for these potential differences by univariate analysis and Kaplan-Meier curves and also by conducting subgroup analysis comparing clinical outcomes time between the two groups. Finally, our findings were based on a retrospective cohort study. The RCT of antiviral drugs with multiple study sites should be planned to better evaluating the effectiveness of antiviral drugs.

Conclusions

In conclusion, no clinical benefit was observed in the severe patients of COVID-19 receiving ribavirin, oseltamivir, abidor, interferon, or Kaletra as treatment. The clinical practitioners should prescribe the antiviral drugs to the severe COVID-19 patients according to their clinical presentations. The antiviral treatment is not recommended to be a regular treatment for COVID-19.

Abbreviations

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; BMI, body mass index; COVID-19, coronavirus disease 2019; CRRT, continuous renal replacement therapy; DIC, disseminated intravascular coagulation; ICU, intensive care unit; IQR, interquartile range; RCT,

randomized clinical trials; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; WHO, World Health Organization.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Zhongnan Hospital of Wuhan University, Wuhan Third Hospital, Union Jiangbei Hospital and the First People's Hospital of Jiangxia District. Written informed consent was obtained from the patient's legal representative in accordance with the ethical standards of the responsible committee on human research.

Consent for publication

Not applicable

Availability of data and materials

Data are available from Dr. Zhigang Zhao, Zhongnan Hospital of Wuhan University at drzhaozhigang@163.com.

Competing interests

We declare no competing interests.

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Authors' contributors

Z.Z., W.X., Y.Z. and Q.H. conceived and designed the study. L.Y., R.L., M.M., Z.H., L.H. and X.X. performed data extraction from the electric medical records system. G.D., H.H., P.W., L.Y., X.W. and X.Z. performed data analysis and figure illustration. X.Z., G.D., H.H. and W.X. discussed the data and wrote the manuscript. Z.Z., W.X., Y.Z. and Q.H. supervised the study. All authors approved the final draft for submission.

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Tables

Table 1 General characteristics of severe COVID-19 patients at baseline.

Characteristics	Total (N=138)	Antiviral treatment		P
		Yes (n=109)	No (n=29)	
Age, mean±SD, years	65.38±12.60	65.43±12.84	65.17±11.88	0.922
Sex				0.201
Female	48 (34.8)	35 (32.1)	13 (44.8)	
Male	90 (65.2)	74 (67.9)	16 (55.2)	
BMI, mean±SD, kg/m²	23.37±3.47	23.35±3.29	23.44±4.06	0.909
Smoking				0.871
Yes	8 (5.8)	7 (6.4)	1 (3.4)	
No	130 (94.2)	102 (93.6)	28 (96.6)	
Co-morbidities				
Hypertension	60 (43.5)	46 (42.2)	14 (48.3)	0.558
Diabetes	24 (17.4)	20 (18.3)	4 (13.8)	0.545
Coronary heart disease	22 (15.9)	16 (14.7)	6 (20.7)	0.617
Renal insufficiency	14 (10.1)	8 (7.3)	6 (20.7)	0.077
Chronic lung disease	10 (7.2)	8 (7.3)	2 (6.9)	1.000
Cerebrovascular disease	10 (7.2)	5 (4.6)	5 (17.2)	0.053
Malignant tumor	8 (5.8)	5 (4.6)	3 (10.3)	0.238
Presence of co-morbidities				0.084
0	52 (37.7)	42 (38.5)	10 (34.5)	
1	40 (29.0)	37 (33.9)	3 (10.3)	
2	32 (23.2)	21 (19.3)	11 (37.9)	
≥3	14 (10.1)	9 (8.2)	5 (17.2)	
Surgery history within 6 months	5 (3.6)	5 (4.6)	0 (0.0)	0.538
Signs and symptoms				
Any	138 (100)	109 (100)	29 (100)	1.000
Fever	117 (84.8)	90 (82.6)	27 (93.1)	0.266
Highest temperature				0.053
37.3-38.0°C	37 (31.6)	24 (26.7)	13 (48.1)	
38.1-39.0°C	64 (54.7)	51 (56.7)	13 (48.1)	
>39.0°C	16 (13.7)	15 (16.7)	1 (3.7)	
Cough or sputum production	111 (80.4)	81 (93.5)	20 (69.0)	0.080
Chest distress/dyspnea	87 (63.0)	67 (61.5)	20 (69.0)	0.457
Fatigue	88 (63.8)	69 (63.3)	19 (65.5)	0.825
Breathlessness or wheezing	73 (52.9)	55 (50.5)	18 (62.1)	0.266
Diarrhea	16 (11.6)	14 (12.8)	2 (6.9)	0.574
Nausea or vomiting	3 (2.2)	2 (1.8)	1 (3.4)	0.510
Ventilation mode at admission				0.229
Inhaling oxygen	121 (87.7)	97 (89.0)	24 (82.7)	
Mechanical ventilation	15 (10.9)	10 (9.2)	5 (17.2)	

Data are presented by number (%) or mean ± SD. P values were calculated by t test, χ^2 test, Mann-Whitney test, or Fisher's exact test, as appropriate. COVID-19, coronavirus disease 2019; SD, standard deviation.

Table 2 Antiviral treatment in severe COVID-19 patients.

Antiviral treatment	Total (N=138)
Drugs and use	109 (79.0)
Ribavirin	50 (36.2)
Dose, median (range), g/d	0.8 (0.4-1.5)
Duration of therapy, median (range), d	5 (1-10)
Oseltamivir	45 (32.6)
Dose, mg/d	150
Duration of therapy, median (range), d	5 (2-13)
Abidor	23 (16.7)
Dose, median (range), g/d	0.4 (0.4-0.6)
Duration of therapy, median (range), d	6 (3-14)
Interferon	16 (11.6)
Dose, median (range), million IU/d	8 (6-10)
Duration of therapy, median (range), d	9 (1-15)
Kaletra (lopinavir/ritonavir)	7 (5.1)
Dose, mg/d	800
Duration of therapy, median (range), d	3 (2-8)
Therapy strategy	
Monotherapy	85 (61.6)
Combined therapy	24 (15.9)

Data are presented by number (%) or median (range). COVID-19, coronavirus disease 2019; d, day(s).

Table 3 Application of other treatments in severe COVID-19 patients.

Treatments	Total (N=138)	Antiviral treatment		P
		Yes (n=109)	No (n=29)	
Antibiotics	133 (96.4)	106 (97.2)	27 (93.1)	0.615
Glucocorticoids	98 (71.0)	80 (73.4)	18 (62.1)	0.232
Initial dose, median (IQR), mg/d	40 (40-80)	40 (40-80)	40 (40-60)	0.554
Duration of therapy, median (IQR), d	4 (2-9)	4 (2-9)	8 (3.75-15.25)	0.014
Vasoactive drugs	42 (30.4)	32 (29.4)	10 (34.5)	0.594
Duration of therapy, median (IQR), d	4 (0.75-9.25)	4 (0.25-7.75)	4.5 (0.75-11)	0.592
High-flow oxygen therapy	45 (32.6)	31 (28.4)	14 (48.3)	0.043
Non-invasive ventilation	46 (33.3)	31 (28.4)	15 (51.7)	0.018
Invasive mechanical ventilation	73 (52.9)	56 (51.4)	17 (58.6)	0.487
Prone position ventilation	12 (8.7)	9 (8.3)	3 (10.3)	1.000
CRRT	7 (5.1)	4 (3.7)	3 (10.3)	0.327
Duration of therapy, median (IQR), d	2 (0-8)	3 (1.25-7.75)	0 (0-0)	0.285

Data are presented by number (%) or median (IQR). *P* values were calculated by χ^2 test, Mann-Whitney test, or Fisher's exact test, as appropriate. COVID-19, coronavirus disease 2019; IQR, interquartile range; d, days.

Table 4 Outcomes and complications of severe COVID-19 patients.

Variables	Total (N=138)	Antiviral treatment		<i>P</i>
		Yes (n=109)	No (n=29)	
Outcomes				
Death	63 (45.7)	48 (44.0)	15 (51.7)	0.460
Duration of hospitalization	11 (7.75-19.25)	11 (6.5-18.0)	16 (8.5-26.0)	0.339
ICU admission	131 (94.9)	106 (97.2)	25 (86.2)	0.053
Mechanical ventilation	73 (52.9)	56 (51.4)	17 (58.6)	0.487
Complications				
Respiratory failure	105 (76.1)	85 (78.0)	20 (69.0)	0.312
ARDS	70 (50.7)	59 (54.1)	11 (37.9)	0.121
Sepsis	48 (34.8)	44 (40.4)	4 (13.8)	0.008
Acute cardiac injury	38 (27.5)	30 (27.5)	8 (27.6)	0.995
Acute liver injury	36 (26.1)	29 (26.6)	7 (24.1)	0.788
Acute kidney injury	31 (22.5)	26 (23.9)	5 (17.2)	0.448
Septic shock	24 (17.4)	22 (20.2)	2 (6.9)	0.093
DIC	11 (8.0)	6 (5.5)	5 (17.2)	0.091
Arrhythmia	10 (7.2)	10 (9.2)	0 (0.0)	0.197
Gastrointestinal bleeding	7 (5.1)	6 (5.5)	1 (3.4)	1.000
Acute cerebrovascular disease	5 (3.6)	5 (4.6)	0 (0.0)	0.538

Data are presented by number (%). *P* values were calculated by χ^2 test or Fisher's exact test, as appropriate. ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; ICU, intensive care unit.

Additional File 1

Table S1 Vital signs and laboratory findings of severe COVID-19 patients at admission.

Fig. S1 Adjusted Kaplan-Meier curves by antiviral treatment stratified by duration of glucocorticoids therapy. (A) Kaplan-Meier curves of survival patients among duration of glucocorticoids therapy ≤ 4 days, (B) Kaplan-Meier curves of survival patients among duration of glucocorticoids therapy > 4 days, (C) Kaplan-Meier curves of deaths among duration of glucocorticoids therapy ≤ 4 days, and (D) Kaplan-Meier curves of deaths among duration of glucocorticoids therapy > 4 days.

Fig. S2 Adjusted Kaplan-Meier curves by antiviral treatments stratified by high-flow oxygen therapy. (A) Kaplan-Meier curves of survival patients without high-flow oxygen therapy, (B) Kaplan-Meier curves of survival patients with high-flow oxygen therapy, (C) Kaplan-Meier

curves of deaths without high-flow oxygen therapy, and (D) Kaplan-Meier curves of deaths with high-flow oxygen therapy.

Fig. S3 Adjusted Kaplan-Meier curves by antiviral treatments stratified by non-invasive ventilation. (A) Kaplan-Meier curves of survival patients without non-invasive ventilation, (B) Kaplan-Meier curves of survival patients with non-invasive ventilation, (C) Kaplan-Meier curves of deaths without non-invasive ventilation, and (D) Kaplan-Meier curves of deaths with non-invasive ventilation.

Figures

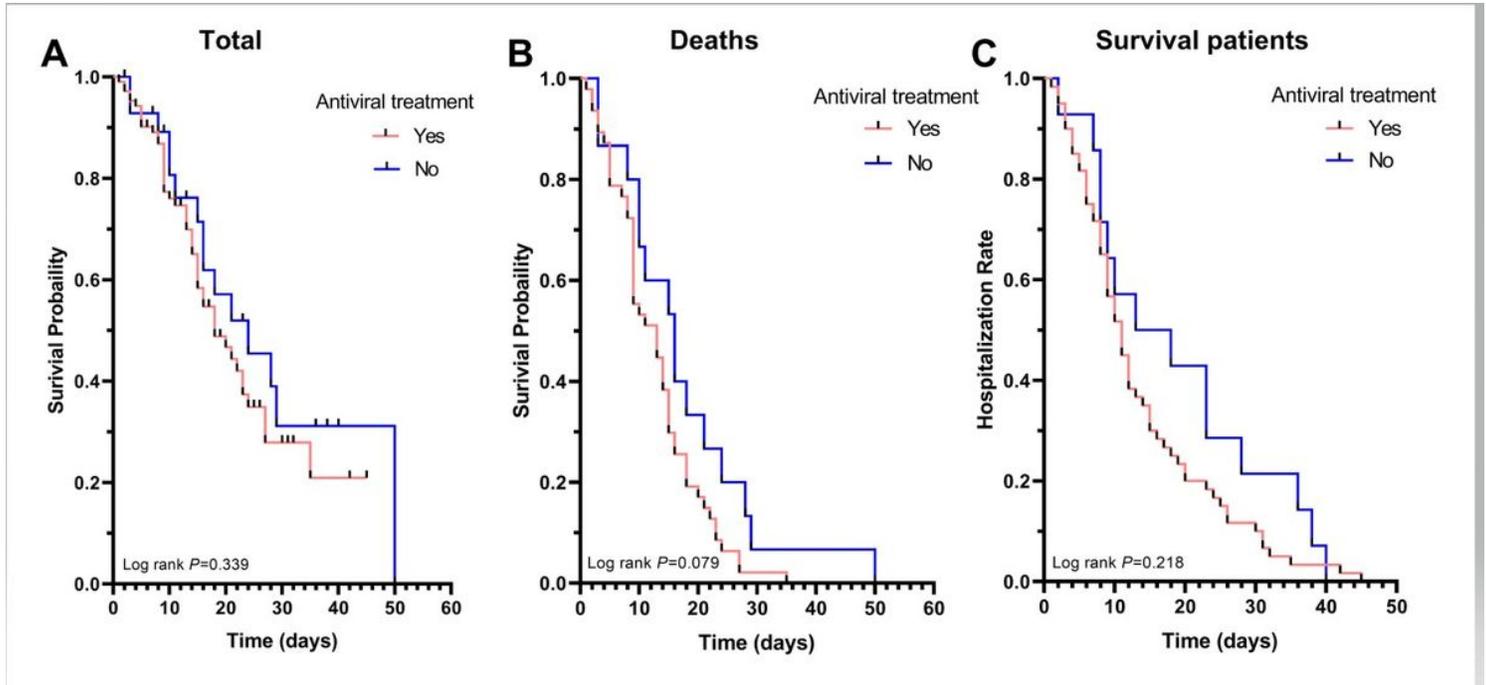


Figure 1

Kaplan-Meier curves by antiviral treatment in total patients (A), deaths (B) and survival patients (C).

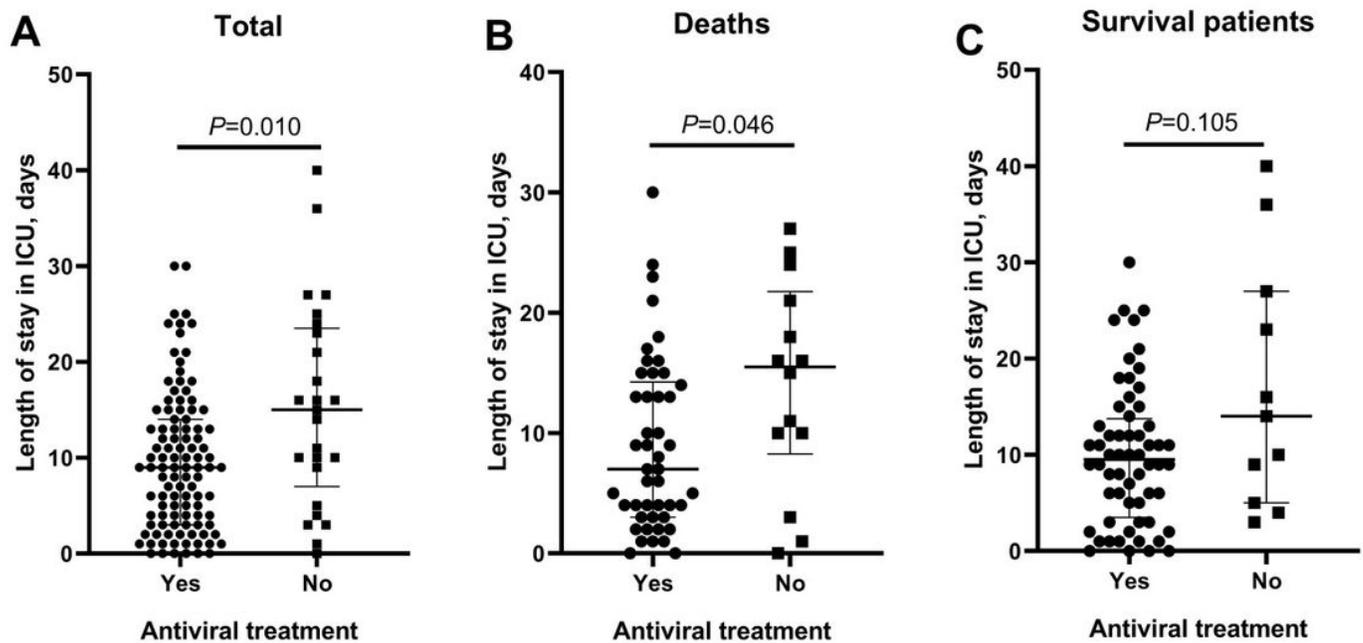


Figure 2

Length of ICU stay by antiviral treatment in total patients (A), deaths (B) and survival patients (C). ICU, intensive care unit.

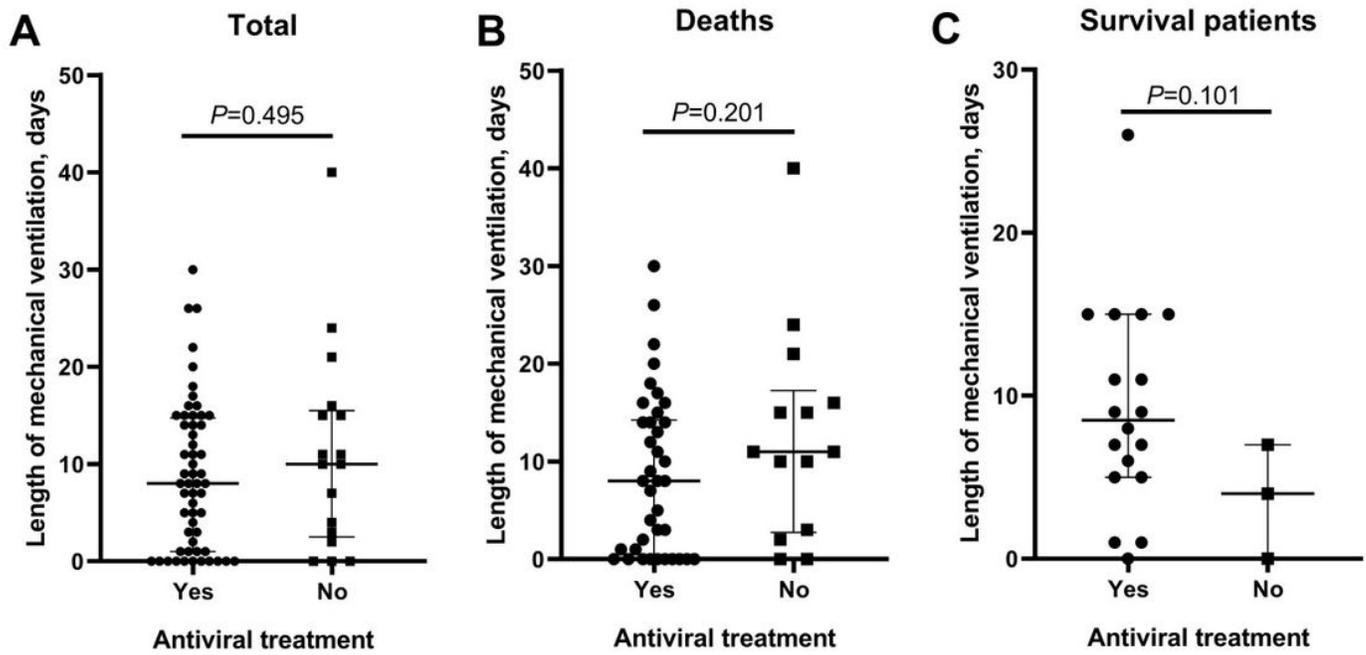


Figure 3

Length of mechanical ventilation of by antiviral treatment in total patients (A), deaths (B) and survival patients (C).

Supplementary Files

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