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Finding the Best Antiviral Regimen for COVID-19: A Double-Center Retrospective Cohort Study of 207 Cases in Hunan, China

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Abstract

Objective: To compare the efficacy of 3/4-drugs' group with 1-drug's or 2-drugs' groups in coronavirus disease 2019 (COVID-19).

Methods: We included 207 patients confirmed with COVID-19. We compared the viral clearance rate and discharge rate at day 7, 14, 21 and 28, and median time of viral clearance and length of hospitalization in patients treated with 3/4, 1 or 2 drugs.

Results: The viral clearance rates of the 3/4-drugs group at day 7, 14 and 21 were significantly lower than those in the 1-drug's or 2-drugs' groups ($P < 0.05$). The median viral clearance days in 3/4-drugs group (13.5 days) were longer than 1-drug's or 2-drugs' groups (both were 9 days) ($P < 0.001$). The patients' discharge rates in the 3/4-drugs group at day 14 and 21 were significantly lower than that in the 1-drug's or 2 drugs' group ($P < 0.05$). The median length of hospitalization in the 3/4-drugs group was 17 days, which was significantly longer than 11 days in the 1-drug group and 13 days in the 2-drug group ($P < 0.05$).

Conclusion: The efficacy of 1 or 2 antiviral drugs was similar in COVID-19, and 3/4-drug regimens were not associated with clinical improvement. Corticosteroid treatment and more serious disease were also risk factors for viral clearance and patients'discharge.

Keywords
COVID-19, antiviral drugs, virus clearance time, length of hospitalization

Introduction

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus emerged in Wuhan,[1] China in December 2019 and soon spread rapidly to every province in China, and Hunan Province, whose location is closest to Wuhan, became the second most affected area. After about 2 months, COVID-19 broke out in Korea, Japan, Europe and America. According to the World Health Organization (WHO), up to July 8, 2020, SARS-CoV-2 had infected >11 million people, resulting in 539 906 deaths worldwide, and these figures are still increasing dramatically.[2]

Most of the antiviral therapies for COVID-19 are those used for severe acute respiratory syndrome coronavirus (SARS-CoV), influenza virus and Middle East respiratory syndrome coronavirus (MERS-CoV), such as lopinavir/ritonavir (LPV/r),[3,4] arbidol,[5] interferon[6] and ribavirin.[7] The guidelines

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for COVID-19 in China do not suggest using ≥3 drugs,[8] but the reasons are unknown. We also have not found sufficient explanation for this, so we carried the present study to compare ≥3 drugs with 1 or 2 drugs, and to identify risk factors associated with viral clearance and length of hospitalization.

Methods

Patients and Ethics

This retrospective cohort study included patients from 2 centers from Changsha Public Health Treatment Center and Xiangtan Central Hospital. Inclusion criteria were: (1) laboratory confirmed inpatients of COVID-19; and (2) available data in medical records, especially the time of diagnosis confirmation, viral clearance, admission to and discharge from hospital, and types of antiviral drugs. Exclusion criteria were: (1) unconfirmed and nonhospitalized patients; and (2) lacking one of the following records: time of diagnosis confirmation, viral clearance, admission to and discharge from hospital, or types of antiviral drugs.

This study was approved by the Institutional Review Board and Ethics Commission of The Second Xiangya Hospital (2020-017). Written informed consent was waived by the Ethics Commission for retrospective analysis and emerging infectious diseases.

Data Collection

We retrospectively collected the data for COVID-19 patients from the above 2 medical centers. The first patient was admitted to hospital on January 24, 2020 and the last patient was discharged on March 14, 2020. The reviewed data included the basic epidemiological, clinical and laboratory data.

Diagnosis of COIVD-19

Diagnosis and severity of COVID-19 were according to "Diagnosis and Treatment Protocol for Novel Coronavirus Infection-Induced Pneumonia (7th version)" in China.[8] Confirmation of diagnosis was based on the following: (1) SARS-CoV-2 nucleic acid assay of respiratory or blood specimens was positive by real-time reverse transcription polymerase chain reaction (RT-PCR); and (2) high throughput gene sequencing was highly homologous with SARS-CoV-2 in respiratory or blood specimens. RT-PCR was performed according to the WHO protocol.[9]

Treatment

Antiviral drugs were given after diagnosis of COVID-19 was confirmed: arbidol 200 mg every 8 h; LPV/r 400 mg/100 mg every 12 h; interferon-α 5 MU in 2 ml normal saline via aerosol inhalation every 12 h; and novaferon 20 μg injected intramuscularly every 12 h. All of the patients received the best supportive care and symptomatic treatment, if necessary, such as oxygen support, mechanical ventilation, extracorporeal membrane oxygenation, antibiotics, antifungals, and corticosteroids.

Outcomes

The primary outcomes were viral clearance rate at day 7, 14, 21 and 28 and median days of viral clearance. Viral clearance was confirmed by 2 continuous negative detections of SARS-CoV-2 by RT-PCR at a 24-h interval. If there were 2 continuous negative detections, the first occasion was defined as the viral clearance time. The secondary outcomes were the patients' discharge rate at day 7, 14, 21 and 28 and median days of hospitalization. The discharge criteria were:[8] (1) at least 2 continuous negative detections of SARS-CoV-2 by RT-PCR at a 24-h interval; (2) no fever for at least 3 days; (3) obvious improvement of respiratory symptoms; and (4) obvious improvement of acute exudative lesions on computed tomography.

Statistical Analysis

Continuous variables of non-normal distribution were expressed as median (interquartile range); continuous variables of 2 groups were compared by Mann–Whitney U test; and continuous variables of ≥3 groups were compared by Kruskal–Wallis H test. Categorical variables were expressed as number (%) and compared by χ^2 test or Fisher's exact test. The Kaplan–Meier curve was used to describe the course of viral clearance and hospitalization. Univariate logistic analysis was used to calculate odds ratio (OR), and multivariate logistic analysis was used to adjust for confounding factors and identify independent risk factors. The statistical analyses were performed using SPSS version 25.0, and $P < 0.05$ was considered to be statistically significant for all test methods.

Results

Patient Characteristics

We included 207 patients, and duration of viral clearance time and length of hospitalization were recorded. There were 60 patients in the 1-drug group (group 1), 91 in the 2-drugs group (group 2), 47 in the 3-drugs and 9 in the 4-drugs group. The latter 2 groups were combined as group 3, owing to the small number of patients in the 4-drugs group. The proportion of mild, moderate, severe and critical patients were 4.3% (9/207), 76.8% (159/207), 14.5% (30/207) and 4.3% (9/207), respectively. In group 1, 18.3% of patients used arbidol, 43.3% LPV/r, and 18.3% novaferon. In group 2, 54.9% of patients used interferon-α + LPV/r, and 17.6% LPV/r + novaferon. In group 3, 42.9% of patients used arbidol + interferon-α + LPV/r, and 16.1%arbidol interferon-α + LPV/r + novaferon.

The rate of lymphocytopenia and corticosteroid treatment were significantly higher in group 3 than in group 2 (Table 1). Intensive care unit (ICU) admission and complications were significantly higher in group 3 than groups 1 + 2 (Supplementary Table 1). There were no other significant differences among the groups. The general features of the groups are presented in Table 1.

Table 1. General Features Among Groups.

Variables	All patients (n = 207)	Group 1 (n = 60)	Group 2 (n = 91)	Group 3 (n = 56)	P
Ages					
≥60	49/207 (23.7%)	13/60 (21.7%)	24/91 (26.4%)	12/56 (21.4%)	0.720
<60	158/207 (86.3%)	47/60 (88.3%)	67/91 (73.6%)	44/56 (78.6%)	
Sex					
Male	98/207 (47.3%)	23/60 (38.3%)	50/91 (54.9%)	25/56 (44.6%)	0.121
Female	109/207 (52.7%)	37/60 (61.7%)	41/91 (45.1%)	31/56 (55.3%)	
Body mass index					
<18.5	7/132 (5.3%)	1/41 (2.4%)	4/91 (45.0%)	2/37 (5.4%)	0.123
18.5-24	68/132 (51.5%)	25/41 (61.0%)	30/91 (33.0%)	13/37 (35.1%)	
>24	57/132 (43.2%)	15/41 (36.6%)	20/91 (22.0%)	22/37 (59.5%)	
Smoking					
Yes	9/207 (4.3%)	1/60 (1.7%)	7/91 (7.7%)	1/56 (1.8%)	0.166
No	198/207 (95.7%)	59/60 (88.3%)	84/91 (92.3%)	55/56 (98.2%)	
Hypertension					
Yes	29/207 (14.0%)	8/60 (13.3%)	15/91 (16.5%)	6/56 (10.7%)	0.610
No	178/207 (86.0%)	52/60 (86.7%)	76/91 (83.5%)	50/56 (89.3%)	
Other comorbidity					
Yes	47/207 (22.7%)	12/60 (20.0%)	23/91 (25.3%)	12/56 (21.4%)	0.725
No	160/207 (77.3%)	48/60 (80.0%)	68/91 (74.7%)	44/56 (78.6%)	
Symptoms					
Fever					
Yes	141/207 (68.1%)	39/60 (65.0%)	60/91 (65.9%)	42/56 (75.0%)	0.430
No	66/207 (31.9%)	21/60 (35.0%)	31/91 (34.1%)	14/56 (25.0%)	
Coughing					
Yes	158/207 (76.3%)	45/60 (75.0%)	66/91 (72.5%)	47/56 (83.9%)	0.276
No	49/207 (23.7%)	15/60 (25.0%)	25/91 (27.5%)	9/56 (16.1%)	
expectoration					
Yes	81/207 (39.1%)	23/60 (38.3%)	31/91 (34.1%)	27/56 (48.2%)	0.230
No	126/207 (60.9%)	37/60 (61.7%)	60/91 (65.9%)	29/56 (51.8%)	
dyspnea					
Yes	47/207 (22.7%)	18/60 (30.0%)	16/91 (17.6%)	13/56 (23.2%)	0.203
No	160/207 (77.3%)	42/60 (70.0%)	75/91 (82.4%)	43/56 (76.8%)	
Diarrhea					
Yes	30/207 (14.5%)	12/60 (20.0%)	11/91 (12.1%)	7/56 (12.5%)	0.355
No	177/207 (85.5%)	48/60 (80.0%)	80/91 (87.9%)	49/56 (87.5%)	
Nausea/Vomit					
Yes	18/207 (8.7%)	6/60 (10.0%)	8/91 (8.8%)	4/56 (7.1%)	0.861
No	189/207 (91.3%)	54/60 (90.0%)	83/91 (91.2%)	52/56 (92.9%)	
Poor appetite					
Yes	24/207 (11.6%)	12/60 (20.0%)	7/91 (7.7%)	5/56 (8.9%)	0.053
No	183/207 (88.4%)	48/60 (80.0%)	84/91 (92.3%)	51/56 (91.1%)	
Fatigue					
Yes	74/207 (35.7%)	27/60 (45.0%)	28/91 (30.8%)	19/56 (33.9%)	0.192
No	133/207 (64.3%)	33/60 (55.0%)	63/91 (69.2%)	37/56 (66.1%)	
Headache					
Yes	20/207 (9.7%)	6/60 (10.0%)	7/91 (7.7%)	7/56 (12.5%)	0.628
No	187/207 (90.3%)	54/60 (90.0%)	84/91 (92.3%)	49/56 (87.5%)	
Complications					
Yes	31/207 (15.0%)	6/60 (10.0%)	12/91 (13.2%)	13/56 (23.2%)	0.112
No	176/207 (85.0%)	54/60 (90.0%)	79/91 (86.8%)	43/56 (76.8%)	
Severe/critical type	39/207 (18.8%)	12/60 (20.0%)	15/91 (16.5%)	12/56 (37.5%)	0.730
Mild/moderate type	168/207 (81.2%)	48/60 (80.0%)	76/91 (83.5%)	44/56 (62.5%)	
ICU	21/207 (10.1%)	5/60 (8.3%)	6/91 (6.6%)	10/56 (17.9%)	0.077
non-ICU	186/207 (89.9%)	55/60 (91.7%)	85/91 (93.4%)	46/56 (82.1%)	
CT findings					
Locations of lesions					
Single lung	24/168 (14.3%)	3/45 (6.7%)	13/75 (17.3%)	8/48 (16.7%)	0.232
Bilateral lung	144/168 (85.7%)	42/45 (93.3%)	62/75 (22.7%)	40/48 (83.3%)	

(continued)

Table 1. (continued)

Variables	All patients (n = 207)	Group 1 (n = 60)	Group 2 (n = 91)	Group 3 (n = 56)	P
Features of lesions					
Ground glass opacities	151/162 (93.2%)	43/48 (89.6%)	66/71 (93.0%)	42/43 (97.7%)	0.322
Consolidative/ mixed opacities	11/162 (6.8%)	5/48 (10.4%)	5/71 (7.0%)	1/43 (2.3%)	
Laboratory findings					
White cell count					
$<4*10^9$/L	74/207 (35.7%)	19/60 (31.7%)	29/91 (31.9%)	26/56 (46.4%)	0.108
4-$10*10^9$/L	127/207 (61.4%)	41/60 (68.3%)	57/91 (62.6%)	29/56 (51.8%)	
$>10*10^9$/L	6/207 (2.9%)	0/60 (0.0%)	5/91 (5.5%)	1/56 (1.8%)	
Neutrophil					
$<2*10^9$/L	42/207 (20.3%)	9/60 (15.0%)	22/91 (24.2%)	11/56 (19.6%)	0.592
2-$7*10^9$/L	158/207 (76.3%)	50/60 (83.3%)	65/91 (71.4%)	43/56 (76.8%)	
$>7*10^9$/L	7/207 (3.4%)	1/60 (1.7%)	4/91 (4.4%)	2/56 (3.6%)	
Lymphocyte					
$<0.8*10^9$/L	55/207 (26.6%)	15/60 (25.0%)	18/91 (19.8%)	22/56 (39.3%)	0.032#
$\geq 0.8*10^9$/L	152/207 (73.4%)	45/60 (75.0%)	73/91 (80.2%)	34/56 (60.7%)	
Hemoglobin					
<110g/L	18/207 (8.7%)	6/60 (10.0%)	7/91 (7.7%)	5/56 (8.9%)	0.883
≥110g/L	189/207 (91.3%)	54/60 (90.0%)	84/91 (92.3%)	51/56 (91.1%)	
Platelet					
$<100*10^9$/L	13/207 (5.8%)	2/60 (3.3%)	7/91 (7.7%)	4/56 (7.1%)	0.546
$\geq 100*10^9$/L	194/207 (94.2%)	58/60 (96.7%)	84/91 (92.3%)	52/56 (92.9%)	
CK					
>170U/L	23/205 (11.2%)	6/59 (10.2%)	7/91 (7.7%)	10/55 (18.2%)	0.144
≤170U/L	182/205 (88.8%)	53/59 (89.8%)	84/91 (92.3%)	45/55 (81.8%)	
CK-MB					
>23U/L	17/205 (8.3%)	3/60 (5.0%)	6/91 (6.6%)	8/54 (14.8%)	0.153
≤23U/L	188/205 (91.7%)	57/60 (95.0%)	85/91 (93.4%)	46/54 (85.2%)	
D-dmier >0.5mg/L					
>0.5mg/L	63/207 (30.4%)	23/60 (38.3%)	20/91 (22%)	20/56 (35.7%)	0.061
≤0.5mg/L	144/207 (69.6%)	37/60 (61.7%)	71/91 (78.0%)	36/56 (64.3%)	
Albumin					
<35g/L	44/178 (24.7%)	15/49 (30.6%)	14/91 (25.3%)	15/47 (31.9%)	0.091
≥35g/L	134/178 (75.3%)	34/49 (69.4%)	68/91 (74.7%)	32/47 (68.1%)	
ALT					
>40U/L	32/207 (15.5%)	10/60 (16.7%)	12/91 (13.2%)	10/56 (17.9%)	0.714
≤40U/L	175/207 (84.5%)	50/60 (83.3%)	79/91 (86.8%)	46/56 (82.1%)	
AST					
>40U/L	26/207 (12.6%)	9/60 (15.0%)	11/91 (12.1%)	6/56 (10.7%)	0.772
≤40U/L	181/207 (87.4%)	51/60 (85.0%)	80/91 (87.9%)	50/56 (89.3%)	
Total bilirubin					
>17.1umol/L	44/207 (21.3%)	12/60 (20.0%)	21/91 (23.1%)	11/56 (19.6%)	0.850
≤17.1umol/L	163/207 (78.7%)	48/60 (80.0%)	70/91 (76.9%)	45/56 (80.4%)	
Creatinine					
>133umol/L	4/207 (1.9%)	2/60 (3.3%)	1/91 (1.1%)	1/56 (1.8%)	0.815
≤133umol/L	203/207 (98.1%)	58/60 (96.7%)	90/91 (98.9%)	55/56 (98.2%)	
LDH					
>250U/L	29/207 (14.0%)	9/60 (15.0%)	8/91 (8.8%)	12/56 (21.4%)	0.097
≤250U/L	178/207 (86.0%)	51/60 (85.0%)	83/91 (91.2%)	44/56 (78.6%)	
CRP					
>10mg/L	115/198 (58.1%)	36/59 (59.3%)	47/83 (56.6%)	32/56 (57.1%)	0.860
≤10mg/L	83/198 (41.9%)	23/59 (40.7%)	36/83 (43.4%)	24/56 (42.9%)	
Procalcitonin					
>0.5ug/L	5/205 (2.4%)	2/60 (3.3%)	2/89 (2.2%)	1/60 (1.7%)	1.000
≤0.5ug/L	200/205 (97.6%)	58/60 (96.7%)	87/89 (97.8%)	55/60 (91.7%)	
Therapy					
Antibiotic					
Yes	98/202 (48.5%)	30/57 (52.6%)	37/90 (31.1%)	31/55 (56.4%)	0.156

(continued)

Table 1. (continued)

Variables	All patients (n = 207)	Group 1 (n = 60)	Group 2 (n = 91)	Group 3 (n = 56)	P
No	104/202 (51.5%)	27/57 (47.4%)	53/90 (58.9%)	24/55 (43.6%)	
Corticosteroid					
Yes	61/204 (29.9%)	18/59 (30.5%)	18/89 (20.2%)	25/56 (44.6%)	0.007#
No	143/204 (70.1%)	41/59 (69.5%)	71/89 (79.8%)	31/56 (55.4%)	
Oxygen therapy					
Yes	165/174 (%)	48/60 (96.7%)	73/77 (94.8%)	44/47 (93.6%)	0.912
No	9/174 (5.2%)	2/60 (3.3%)	4/77 (5.2%)	3/47 (6.4%)	

Group 1: 1 drug.
Group 2: 2 drugs.
Group 3: 3/4 drugs.
CT: Computed tomography.
ALT: Alanine aminotransferase.
AST: Aspartate aminotransferase.
LDH: Lactate dehydrogenase.
CRP: C-responsive protein.
CK: Creatine kinase.
CK-MB: Creatine kinase-MB.
Group 3 VS Group 2: P < 0.05.

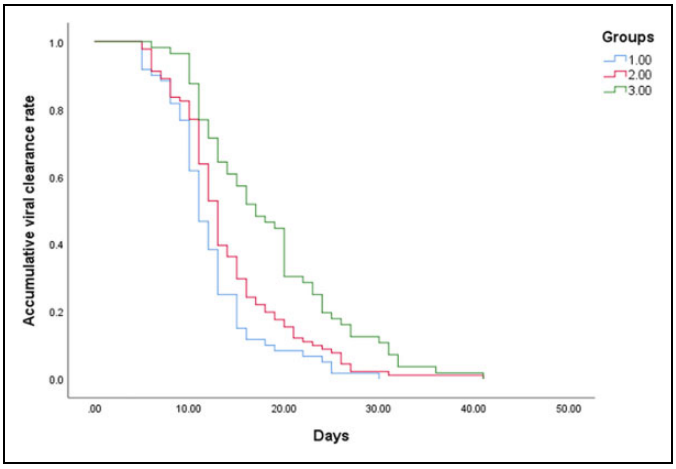

Figure 1. The course of viral clearance after confirmation.

Viral Clearance and Patients' Discharge Rate at Days 7, 14, 21 and 28

The viral clearance rate of group 3 at day 7, 14 and 21 was significantly lower than in group 1 or group 2. At day 28, this rate in group 3 was significantly lower than in groups 1 and 2 (P < 0.05). The viral clearance time in group 3 of 13.5 (9.3–18) days was significantly longer than 9 (6.3–11) days in group 1 and 9 (7–12) days in group 2 (P < 0.001) (Table 2 and Figure 1).

In the subgroup analysis of median viral clearance time, there was no obvious difference among the group 1 subgroups: arbidol (8 days), LPV/r (10 days) and novaferon (9 days) (P = 0.198). In group 2 subgroups, the median viral clearance time for arbidol + LPV/r was 15 days, which was significantly longer than 9 days for interferon-α + LPV/r and 8 days for interferon-α + novaferon (P < 0.05). In group 3 subgroups, the median viral clearance time for arbidol + interferon-α + LPV/r was 14.5 days and 14 days for arbidol + interferon-α + LPV/r + novaferon, which was significantly longer than 9.5 days for arbidol + LPV/r + novaferon (P < 0.05) (Supplementary Table 2).

The patients' discharge rate in group 3 at days 14 and 21 was significantly shorter than in groups 1 and 2, and at day 28, this rate in group 3 was lower than in group 2 (P < 0.05). The length of hospitalization in group 3 was 17 (12–23.8) days, which was significantly longer than 13 (11–16) days in group 2 and 11 (10–14.5) days in group 1. The length of hospitalization in group 2 was significantly longer than in group 1 (P < 0.05) (Table 2 and Figure 2). The mortality rate did not differ significantly among the groups.

Factors Associated With Viral Clearance and Patients' Discharge Rate

We chose day 14 to analyze risk factors associated with viral clearance (79.7% of patients obtained viral clearance), and chose day 21 to analyze risk factors associated with discharge rate (time of hospitalization was longer than viral clearance). Complications, severe/critical disease, ICU admission, lymphocytopenia, and antibiotic and corticosteroid treatment were all associated with lower viral clearance rate and patients' discharge rate. Additionally, higher alanine aminotransferase and lactate dehydrogenase were associated with significantly lower viral clearance rate, and higher total bilirubin was associated with significantly lower discharge rate (P < 0.05) (Table 3).

Univariate logistic regression showed that all of the above variables were significant. After adjusting in multivariate logistic model, group 3, ICU admission and corticosteroid treatment were independent risk factors for viral clearance; and group 3, complications, total bilirubin and corticosteroid treatment were independent risk factors for patients' discharge (Table 4).

In order to identify whether group 3 was actually independently related to poor viral clearance, or it due to relate to the

Table 2. Viral Clearance and Discharged Rate Among Groups at Different Days.

Viral clearance rate	Total (n = 207)	Group 1 (n = 60)	Group 2 (n = 91)	Group 3 (n = 56)	P
Day 7	49 (23.7%)	22 (36.7%)	23 (25.3%)	4 (7.1%)	0.001[&]
Day14	165 (79.7%)	53 (88.3%)	78 (85.7%)	34 (60.7%)	<0.001[&]
Day21	190 (91.7%)	57 (95.0%)	87 (95.6%)	46 (82.1%)	0.017[&]
Day 28	202 (97.6%)	60 (100%)	90 (98.9%)	52 (92.9%)	0.031[△]
Days of clearance median(IQR)	10 (8-13)	9 (6.3-11)	9 (7-12)	13.5 (9.3-18)	<0.001[#]
Discharge rate					
Day7	18 (8.7%)	7 (11.7%)	10 (11.0%)	1 (1.8%)	0.098
Day14	124 (59.9%)	45 (75.0%)	58 (63.7%)	21 (37.5%)	<0.001[&]
Day21	174 (84.1%)	55 (91.7%)	80 (87.9%)	39 (69.6%)	0.002[&]
Day 28	197 (95.2%)	59 (98.3%)	89 (97.8%)	49 (87.5%)	0.014[◇]
Days of hospitalization median(IQR)	13 (11-18)	11 (10-14.5)	13 (11-16)	17 (12-23.8)	<0.001*
Death	3 (4.7%)	0 (0%)	1 (1.1%)	2 (3.6%)	0.354

Group 1: 1 drug.
Group 2: 2 drugs.
Group 3: 3/4 drugs.
&: Group 3 VS Group 1/Group 2, both P < 0.05, Group 1 VS Group 2:P > 0.05.
△: Group 3 VS Group 1 + group 2: P = 0.029.
◇: Group 3VS Group 2: P = 0.030.
[#]Group 3 VS group 2/Group 1:P < 0.001.
*Group 3 VS Group 1, Group 3VS Group 2, Group 1 VS Group 2, all P < 0.05.
IQR: interquartile range.

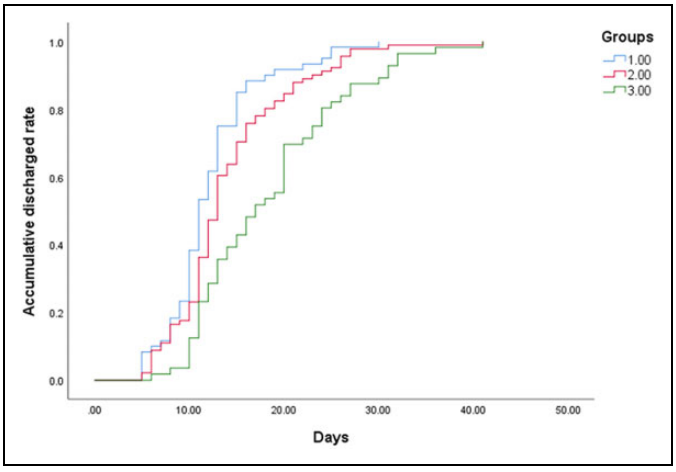

Figure 2. The course of patients' discharge after admission hospital.

patients type that is more serious, we carried out subgroup analyses in the moderate COVID-19 group (accounted for 76.8% of patients). The viral clearance rate at day 14 and median clearance time of the 3/4-drugs group (70% and 12 days) were still significantly poorer than those of the 1/2-drugs groups (89.1% and 9 days) (P < 0.05). After adjusting for lymphocytopenia and corticosteroid treatment (only 2 confounder factors in the moderate group), and type of drugs in the logistic multivariate model, the 3/4-drugs group still existed statistical significance (adjusted OR = 3.14, P = 0.013). Further subgroup analysis of the 3/4-drugs group showed that arbidol + interferon-α + LPV/r (median: 12 days) and arbidol + interferon-α + LPV/ + novaferon (median: 14 days) were the main "culprits" leading to longer clearance time. The median time of the other 2 regimens arbidol + LPV/r + novaferon and interferon-α + LPV/r + novaferon was both 9.5 days.

Discussion

We investigated the efficacy of different antiviral drugs in COVID-19 and identified risk factors associated with viral clearance or length of hospitalization. In group 1, there was no significant difference in viral clearance or length of hospitalization among arbidol, LPV/r and novaferon. Novaferon is a new type of interferon, which has been used for treatment of hepatitis B.[10] There were also no significant difference in viral clearance between groups 1 and 2, but both of them were superior to group 3. Previously, we thought that this situation was because the patients in group 3 had more serious disease, but after we analyzed the moderate COVID-19 group, we found that the 3/4-drugs group still independently associated with poor viral clearance. Furthermore, we found that arbidol + interferon-α + LPV/r and 4-drugs regimens were the main causes leading to longer viral clearance, and viral clearance with the other 2 regimens was equivalent to that in the 1/2-drugs groups. It is not clear why 3/4 drugs were not superior to 1 or 2 drugs, and we offer the following explanation.

Firstly, the present evidence at least does not favor treatment with 3 drugs. One study compared hydroxychloroquine + arbidol + interferon-α with LPV/arbidol + interfere- on-α in 15 cases of COVID-19, and viral clearance rates at day 7 (86.7% vs 93.3%) and day 14 (both 100%) were similar.[11] Another study in 75 cases compared hydroxylchloroquine + standard-of-care with standard-of-care; standard-of-care was according

Table 3. Factors Associated Viral Clearance and Patients' Discharged Rate Among Groups.

Variables	All patients	Day 14 viral clearance rate		P	Day 21 discharge rate		P
General features	(n = 207)	Yes (n = 165)	No (n = 42)		Yes (n = 174)	No (n = 33)	
Ages							
≥60	49/207 (23.7%)	37/165 (22.4%)	12/42 (28.6%)	0.403	44/174 (25.3%)	5/33 (15.2%)	0.209
<60	158/207 (66.3%)	128/165 (77.6%)	30/42 (71.4%)		130/174 (74.7%)	28/33 (84.8%)	
Sex							
Male	98/207 (47.3%)	76/165 (46.1%)	22/42 (52.4%)	0.464	80/174 (46.0%)	18/33 (54.5%)	0.366
Female	109/207 (52.7%)	89/165 (53.9%)	20/42 (47.6%)		94/174 (54.0%)	15/33 (45.5%)	
Body mass index							
<18.5	7/132 (5.3%)	6/132 (4.5%)	1/25 (4.0%)	0.844	6/116 (5.2%)	1/16 (6.3%)	0.426
18.5-24	68/132 (51.5%)	56/132 (42.4%)	12/25 (48.0%)		62/116 (53.4%)	6/16 (37.5%)	
>24	57/132 (43.2%)	45/132 (34.1%)	12/25 (48.0%)		48/116 (41.4%)	9/16 (56.3%)	
Smoking							
Yes	9/207 (4.3%)	8/165 (4.8%)	1/42 (2.4%)	0.782	9/174 (5.2%)	0/33 (0%)	0.384
No	198/207 (95.7%)	157/165 (95.2%)	41/42 (97.6%)		165/174 (94.8%)	33/33 (100%)	
Hypertension							
Yes	29/207 (14.0%)	24/165 (14.5%)	5/42 (11.9%)	0.660	25/174 (14.4%)	4/33 (12.1%)	0.946
No	178/207 (86.0%)	141/165 (85.5%)	37/42 (88.1%)		149/174 (85.6%)	29/33 (87.9%)	
Other comorbidity							
Yes	47/207 (22.7%)	38/165 (23.0%)	9/42 (21.4%)	0.825	39/174 (22.4%)	8/33 (24.2%)	0.818
No	160/207 (77.3%)	127/165 (77.0%)	33/42 (78.6%)		135/174 (77.6%)	25/33 (75.8%)	
Symptoms							
Fever							
Yes	141/207 (68.1%)	111/165 (67.3%)	30/42 (71.4%)	0.606	117/174 (67.2%)	24/33 (72.7%)	0.535
No	66/207 (31.9%)	54/165 (32.7%)	12/42 (28.6%)		57/174 (32.8%)	9/33 (27.3%)	
Coughing							
Yes	158/207 (76.3%)	126/165 (76.4%)	32/42 (76.2%)	0.981	133/174 (76.4%)	25/33 (75.8%)	0.933
No	49/207 (23.7%)	39/165 (23.6%)	10/42 (23.8%)		41/174 (23.6%)	8/33 (24.2%)	
Expectoration							
Yes	81/207 (39.1%)	62/165 (37.6%)	19/42 (45.2%)	0.364	67/174 (38.5%)	14/33 (42.4%)	0.672
No	126/207 (60.9%)	103/165 (62.4%)	23/42 (54.8%)		107/174 (61.5%)	19/33 (57.6%)	
Dyspnea							
Yes	47/207 (22.7%)	35/165 (21.2%)	12/42 (28.6%)	0.309	37/174 (21.3%)	10/33 (30.3%)	0.256
No	160/207 (77.3%)	130/165 (18.2%)	30/42 (71.4%)		137/174 (78.7%)	23/33 (69.7%)	
Diarrhea							
Yes	30/207 (14.5%)	25/165 (15.2%)	5/42 (11.9%)	0.594	23/174 (13.2%)	7/33 (21.2%)	0.354
No	177/207 (85.5%)	140/165 (84.8%)	37/42 (88.2%)		151/174 (86.8%)	26/33 (78.8%)	
Nausea/Vomit							
Yes	18/207 (8.7%)	16/165 (9.7%)	2/42 (4.8%)	0.480	16/174 (9.2%)	2/33 (6.1%)	0.803
No	189/207 (91.3%)	149/165 (90.3%)	40/42 (95.2%)		158/174 (80.8%)	31/33 (93.9%)	
Poor appetite							
Yes	24/207 (11.6%)	18/165 (10.9%)	6/42 (14.3%)	0.734	21/174 (12.1%)	3/33 (10.0%)	0.847
No	183/207 (88.4%)	147/165 (89.1%)	36/42 (85.7%)		153/174 (87.9%)	30/33 (90.0%)	
Fatigue							
Yes	74/207 (35.7%)	62/165 (37.6%)	12/42 (28.6%)	0.277	64/174 (38.5%)	10/33 (30.3%)	0.476
No	133/207 (64.3%)	103/165 (62.4%)	30/42 (71.4%)		110/174 (61.5%)	23/33 (69.7%)	
Headache							
Yes	20/207 (9.7%)	18/165 (10.9%)	2/42 (4.8%)	0.362	18/174 (10.3%)	2/33 (6.1%)	0.658
No	187/207 (90.3%)	147/165 (89.1%)	40/42 (95.2%)		156/174 (89.7%)	31/33 (93.9%)	
Complications							
Yes	31/207 (15.0%)	17/165 (10.3%)	14/42 (33.3%)	<0.001	16/174 (9.2%)	15/33 (45.5%)	<0.001
No	176/207 (85.0%)	148/165 (89.7%)	28/42 (66.7%)		158/174 (90.8%)	18/33 (54.5%)	
Severe/critical type	39/207 (18.8%)	23/207 (59.0%)	16/42 (38.1%)	<0.001	28/174 (16.1%)	11/33 (33.3%)	0.020
Mild/moderate type	168/207 (81.2%)	142/207 (83.9%)	26/42 (61.9%)		146/174 (83.9%)	22/33 (66.7%)	
ICU	21/207 (10.1%)	9/165 (5.5%)	12/42 (28.6%)	<0.001	11/174 (6.3%)	10/33 (30.7%)	<0.001
non-ICU	186/207 (89.9%)	156/165 (94.5%)	30/42 (71.4%)		163/174 (93.7%)	23/33 (69.7%)	
CT findings							
Locations of lesions							
Single lung	24/168 (14.3%)	20/131 (15.3%)	4/37 (10.8%)		22/143 (15.4%)	2/25 (8.0%)	0.507
Bilateral lung	144/168 (85.7%)	111/131 (84.7%)	33/37 (89.2%)	0.494	121/143 (84.6%)	23/25 (92.0%)	

(continued)

Table 3. (continued)

Variables	All patients	Day 14 viral clearance rate		P	Day 21 discharge rate		P
Features of lesions							
Ground glass opacities	151/162 (93.2%)	122/131 (93.1%)	29/31 (93.5%)	1.000	131/141 (92.9%)	20/21 (95.2%)	1.000
Consolidative/ mixed opacities	11/162 (6.8%)	9/131 (6.9%)	2/31 (6.5%)		10/141 (7.1%)	1/21 (4.8%)	
Laboratory findings							
White cell count							
<4*10^9/L	74/207 (35.7%)	56/165 (33.9%)	18/42 (42.9%)	0.573	58/174 (33.3%)	16/33 (48.5%)	0.182
4-10*10^9/L	127/207 (61.4%)	104/165 (64.2%)	23/42 (54.8%)		111/174 (63.8%)	16/33 (48.5%)	
>10*10^9/L	6/207 (2.9%)	5/165 (3.0%)	1/42 (2.4%)		5/174 (2.9%)	1/33 (3.0%)	
Neutrophil							
<2*10^9/L	42/207 (20.3%)	35/165 (21.2%)	7/42 (16.7%)	0.714	33/174 (19.0%)	9/33 (27.3%)	0.324
2-7*10^9/L	158/207 (76.3%)	125/165 (75.8%)	33/42 (78.6%)		136/174 (78.2%)	22/33 (69.7%)	
>7*10^9/L	7/207 (3.4%)	5/165 (3.0%)	2/42 (4.8%)		5/174 (2.8%)	2/33 (6.1%)	
Lymphocyte							
<0.8*10^9/L	55/207 (26.6%)	38/165 (23.0%)	17/42 (40.5%)	0.022	37/174 (21.3%)	18/33 (54.5%)	<0.001
≥0.8*10^9/L	152/207 (73.4%)	127/165 (77.0%)	25/42 (59.5%)		137/174 (78.7%)	15/33 (45.5%)	
Hemoglobin							
<110g/L18	18/207 (8.7%)	12/165 (7.3%)	6/42 (14.3%)	0.257	13/174 (7.5%)	5/33 (15.2%)	0.272
≥110g/L189	189/207 (91.3%)	153/165 (92.7%)	36/42 (85.7%)		161/174 (92.5%)	28/33 (84.8%)	
Platelet							
<100*10^9/L	13/207 (6.3%)	8/165 (4.8%)	5/42 (11.9%)	0.185	9/174 (5.2%)	4/33 (12.1%)	0.264
≥100*10^9/L	194/207 (93.7%)	157/165 (95.2%)	37/42 (88.1%)		165/174 (94.8%)	29/33 (87.9%)	
CK							
>170U/L	23/205 (11.2%)	17/165 (10.3%)	6/41 (14.6%)	0.619	19/174 (10.9%)	4/33 (12.1%)	1.000
≤170U/L	182/205 (88.8%)	147/165 (89.7%)	35/41 (85.4%)		153/174 (89.1%)	29/33 (87.9%)	
CK-MB							
>23U/L	17/205 (8.2%)	12/165 (7.3%)	5/39 (12.8%)	0.414	13/174 (7.5%)	4/33 (12.1%)	0.599
≤23U/L	188/205 (91.8%)	154/165 (92.7%)	34/39 (87.2%)		159/174 (92.5%)	29/33 (87.9%)	
D-dmier							
>0.5mg/L	63/207 (30.4%)	50/165 (30.3%)	13/40 (32.5%)	0.752	51/174 (29.3%)	12/33 (36.4%)	0.419
≤0.5mg/L	144/207 (69.6%)	117/165 (69.7%)	27/40 (67.5%)		123/174 (70.7%)	21/33 (63.6%)	
Albumin							
<35g/L	44/178 (24.7%)	32/140 (21.9%)	12/38 (38.1%)	0.269	35/152 (23.0%)	9/26 (34.6%)	0.206
≥35g/L	134/178 (75.3%)	108/140 (78.1%)	26/38 (61.9%)		117/152 (77.0%)	17/26 (65.4%)	
ALT							
>40U/L	32/207 (15.5%)	21/165 (65.6%)	11/42 (26.2%)	0.031	25/174 (14.4%)	7/33 (21.2%)	0.319
≤40U/L	175/207 (84.5%)	144/165 (82.3%)	31/42 (73.8%)		149/174 (85.6%)	26/33 (78.8%)	
AST							
>40U/L	26/207 (12.6%)	19/165 (11.5%)	7/42 (16.7%)	0.330	22/174 (12.6%)	4/33 (12.1%)	1.000
≤40U/L	181/207 (87.4%)	147/165 (88.5%)	34/42 (83.3%)		152/174 (87.4%)	29/33 (87.9%)	
Total bilirubin							
>17.1umol/L	44/207 (21.3%)	35/165 (21.2%)	9/42 (21.4%)	0.976	32/174 (18.4%)	12/33 (36.4%)	0.021
≤17.1umol/L	163/207 (78.7%)	130/165 (78.8%)	33/42 (78.6%)		142/174 (71.6%)	21/33 (63.6%)	
Creatinine							
>133umol/L	4/207 (1.9%)	2/165 (1.2%)	2/42 (4.8%)	0.182	2/174 (1.1%)	2/33 (6.1%)	0.120
≤133umol/L	203/207 (98.1%)	163/165 (88.8%)	40/42 (95.2%)		172/174 (98.9%)	31/33 (93.9%)	
LDH							
>250 U/L	29/207 (14.0%)	19/165 (11.5%)	10/42 (23.8%)	<0.001	22/174 (12.6%)	7/33 (21.2%)	0.305
≤250U/L	178/207 (86.0%)	146/165 (88.5%)	32/42 (76.2%)		152/174 (87.4%)	26/33 (78.8%)	
CRP							
>10mg/L	115/198 (58.1%)	92/156 (59.0%)	23/42 (54.8%)	0.623	94/169 (55.6%)	21/30 (73.7%)	0.090
≤10mg/L	83/198 (41.9%)	64/156 (41.0%)	19/42 (45.2%)		75/169 (44.4%)	8/30 (26.7%)	
Procalcitonin							
>0.5ug/L	5/205 (2.4%)	4/165 (2.4%)	1/40 (2.5%)	1.000	3/172 (1.7%)	2/33 (6.1%)	0.184
≤0.5ug/L	200/205 (97.6%)	161/165 (97.6%)	39/40 (97.5%)		169/172 (98.3%)	31/33 (93.9%)	
Therapy							
Antibiotic							
Yes	98/202 (48.5%)	72/161 (44.7%)	26/41 (63.4%)	0.032	75/169 (44.4%)	23/33 (69.7%)	0.008
No	104/202 (51.5%)	89/161 (55.3%)	15/41 (36.6%)		94/169 (55.6%)	10/33 (30.3%)	

(continued)

Table 3. (continued)

Variables	All patients	Day 14 viral clearance rate		P	Day 21 discharge rate		P
Corticosteroid							
Yes	61/204 (30.3%)	38/163 (62.3%)	23/41 (48.8%)	<0.001	42/171 (24.6%)	19/33 (57.6%)	<0.001
No	143/204 (69.7%)	125/163 (37.7%)	18/41 (43.9%)		129/171 (75.4%)	14/33 (42.4%)	
Oxygen support							
Yes	165/174 (94.8%)	132/139 (95.0%)	33/35 (94.3%)	1.000	143/152 (94.1%)	22/22 (100%)	0.511
No	9/174 (5.2%)	7/139 (5.0%)	2/35 (5.7%)		9/152 (5.9%)	0/22 (0.0%)	

CT: Computed tomography.
ALT: Alanine aminotransferase.
AST: Aspartate aminotransferase.
LDH: Lactate dehydrogenase.
CRP: C-responsive protein.
CK: Creatine kinase.
CK-MB: Creatine kinase-MB.

Table 4. Logistic Analysis of Factors Associated Viral Clearance and Patients' Discharged Rate.

Factors associated viral clearance at day 14

Variables	Univariate analysis OR (95%CI)	P	Multivariate analysis OR (95%CI)	P
3/4 drugs	4.24 (2.08-8.65)	<0.001	3.07 (1.42-6.65)	0.004
Complications	4.35 (1.93-9.83)	<0.001	-	0.402
Severe/critical	3.80 (1.77-8.15)	0.001	-	0.855
ICU admission	6.93 (2.69-17.90)	<0.001	3.83 (1.31-11.16)	0.014
Lymphocyte $<0.8*10^9$/L	2.60 (1.27-5.29)	0.009	-	0.633
ALT>40U/L	2.43 (1.07-5.56)	0.035	-	0.330
LDH>250U/L	2.40 (1.02-5.65)	0.045	-	0.834
Antibiotic	2.14 (1.06-4.35)	0.035	-	0.928
Corticosteroid	4.20 (2.06-8.20)	<0.001	2.52 (1.12-5.67)	0.026

Factors associated patients' discharge at day 21.

Variables	Univariate analysis OR (95%CI)	P	Multivariate analysis OR (95%CI)	P
3/4 drugs	3.68 (1.70-7.94)	0.010	2.99 (1.26-7.14)	0.013
Complications	8.23 (3.49-19.38)	<0.001	5.10 (1.96-13.25)	0.001
Severe/critical	2.61 (1.14-5.97)	0.023	-	0.118
ICU admission	6.44 (2.46-16.85)	<0.001	-	0.910
Lymphocyte $<0.8*10^9$/L	4.44 (2.04-9.65)	<0.001	-	0.134
Total bilirubin >17.1umol/L	2.54 (1.13-5.68)	0.024	2.89 (1.14-7.35)	0.025
Antibiotic	2.88 (1.29-6.43)	0.010	-	0.307
Corticosteroid	4.17 (1.90-9.03)	<0.001	2.56 (1.03-6.19)	0.043

ALT: Alanine aminotransferase.
LDH: Lactate dehydrogenase.
ICU: Intensive care unit.

to COVID-19 guidelines in China (1 or 2 antiviral drugs).[12] The viral clearance rates at day 4, 7, 10, 14, 21 and 28 (85.4% vs 81.3%), median clearance time (8 days vs 7 days) and symptom alleviation rate at day 28 (59.9% vs 66.6%) were all similar. Another trial in 199 cases of LPV/r in addition to standard care showed that the median time to clinical improvement (both 16 days), mortality at 28 days (19.2% vs 25.0%) and viral clearance rate were all similar.[13]

Secondly, both SARS and COVID-19 are acute virus infections that have self-limiting features in some mild/moderate cases.[14] A recent clinical trial compared LPV/r or arbidol with no antiviral treatment.[15] The mean time to viral clearance (9.0 vs 9.1 vs 9.3 days), viral clearance rate at different times, and clinical improvement were all similar among the 3 groups.[15]

Thirdly, adding more antiviral drugs may bring more risk to patients. In one study of COVID-19, median viral clearance time of 3 drugs was longer than for 2 drugs (4 vs 2 days).[11] In a retrospective study of MERS, interferon + ribavirin compared with no ribavirin/interferon increased 90-day mortality rate (73.6% vs 61.5%), and the adjusted hazard ratio in the Cox model remained significant.[16]

Fourthly, interferon is also an inflammatory factor and can enhance immunoreactivity. It has been shown that adding interferon to treatment of middle- and late-stage SARS patients may cause disease deterioration,[14] and interferon can stimulate expression of angiotensin-converting enzyme 2, which can accelerate replication and spread of COVID-19.[17]

Fifthly, patients in different studies have diverse characteristics. For example, in China, remdesivir did not have a significant effect on time to clinical improvement,[18] but in the US, it significantly shortened recovery time.[19] Nevertheless, in China, time to clinical improvement was faster in patients with symptom duration $\leq$10 days.[18]

Our study showed that corticosteroid treatment delayed viral clearance and length of hospitalization. On January 28, 2020, WHO had already declared that present evidence did not support corticosteroid treatment for COVID-19 lung injury.[20] Corticosteroids may prevent viral clearance and delay hospitalization through inhibiting immunity. One study of patients with critical MERS showed that corticosteroid treatment delayed viral clearance, and patients

required more mechanical ventilation, vasopressors, and renal replacement therapy.[21] A meta-analysis showed that corticosteroid treatment was harmful in SARS patients, including more viremia, complications, and psychosis.[22] A systematic review and meta-analysis of influenza found that corticosteroid treatment increased mortality and length of stay in ICU.[23]

We found no significant relationship between total bilirubin and disease severity (Supplementary Table 6), so higher total bilirubin was an independent risk factor for prolonged hospitalization. However, complications were associated with patients who had more serious disease.

Our study had several limitations. (1) Although we used a multivariate logistic model to adjust confounders, we could not exclude potential confounding factors. (2) The limited number of patients in the 3/4-drugs group restricted the statistical power of the subgroup analysis. (3) We did not analyze adverse effect of drugs, owing to insufficient data. Most cases of adult respiratory distress syndrome occurred within 4 days (median 1 day) after admission to hospital in our study, so it did not relate to drug efficacy. (4) There were few fatal cases in our study, so there were insufficient data to analyze mortality. (5) The current study did not involve remdesivir, which was not approved in China. Remdesivir can inhibit formation of viral RNA in many viruses such as Ebola virus, Nipah virus, MERS-CoV, SARS-CoV and SARS-CoV-2.[24]

In conclusion, our study showed that the efficacy of 1 or 2 antiviral drugs was similar in COVID-19, and 3/4-drug regimens were not associated with clinical improvement. Conversely, some regimens of 3/4 drugs might bring poor clinical outcomes. Corticosteroid treatment and more serious disease conditions were both risk factors for viral clearance and length of hospitalization. The current study may provide some reference values for clinicians, and changed the thinking that more antiviral drugs may bring better efficacy. It also benefits patients and reduces hospitalization cost, thus saving medical resources.

Authors' Note

Xingsheng Hu and Chunhong Hu contributed equally. The primary data of this article are available from the corresponding author upon reasonable request.

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Supplemental Material

Supplemental material for this article is available online.

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