Treatment Response to Hydroxychloroquine, Lopinavir–Ritonavir, and Antibiotics for Moderate COVID-19: A First Report on the Pharmacological Outcomes from South Korea

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Abstract

Background: No consensus or evidence-based guideline currently exists for pharmacological therapy against Coronavirus Disease 2019 (COVID-19). While South Korea has been relatively successful in managing the pandemic, its management of confirmed cases and treatment outcomes have not been reported to date.

Methods: A retrospective cohort study of the 358 laboratory-confirmed SARS-CoV-2 – or COVID-19 - patients was conducted. Of these patients, 270 adult patients met inclusion criteria and were included in our analyses. The primary endpoints were time to viral clearance and clinical improvement. The mean duration to viral clearance and clinical improvements were displayed as bar-plots to visualize treatment responses.

Results: Ninety-seven moderate COVID-19 patients were managed with hydroxychloroquine (HQ) plus antibiotics (n = 22), lopinavir-ritonavir (Lop/R) plus antibiotics (n = 35), or conservative treatment (n = 40). Time to viral clearance, as signified by negative conversion on PCR, after initiation of treatment was significantly shorter with HQ plus antibiotics compared to Lop/R plus antibiotics (hazard ratio [HR], 0.49; 95% confidence interval [95% CI], 0.28 to 0.87) or conservative treatments (HR, 0.44; 95% CI, 0.25 to 0.78). Hospital stay duration after treatment was also shortest for patients treated with HQ plus antibiotics compared to other treatment groups. Subgroup analysis revealed that mean duration to viral clearance was significantly reduced with adjunctive use of antibiotics compared to monotherapy (HR 0.81, 95% CI, 0.70 to 0.93). While both HQ and Lop/R showed side effects including nausea, vomiting, and elevation of liver transaminases, none were serious.

Conclusion: This first report on pharmacological management of COVID-19 from South Korea revealed that HQ with antibiotics was associated with better clinical outcomes in terms of viral clearance, hospital stay, and cough symptom resolution compared to Lop/R with antibiotics or conservative treatment. The effect of Lop/R with antibiotics was not superior to conservative management. The adjunct use of the antibiotics may provide additional benefit in COVID-19 management but warrants further evaluation.

Introduction

As of May 6th 2020, over 3,500,000 confirmed cases and over 245,000 deaths due to Coronavirus Disease 2019 (COVID-19) were reported by the World Health Organization (WHO)[1]. The causative virus of this pandemic, SARS-CoV-2, presents an unprecedented challenge to healthcare systems worldwide, but definitive treatment remains unknown due to the lack of the clear understanding of the pathogenesis of the disease or the nature of its causative virus [2]. Randomized controlled trials (RCTs) are yet to demonstrate any evidence supporting a particular pharmacologic treatment strategy for patients with confirmed SARS-CoV-2 infection [3].

Based on a recent study from China, about 80% of COVID-19 patients show non-severe symptoms[4]. Thus, it is relevant to a large number of patients to investigate potential drugs that may be effective for patient with non-severe disease. Numerous hospitals in South Korea have experience treating moderate COVID-19 with three main management protocols; standard supportive care, hydroxychloroquine (HQ), and lopinavir-ritonavir (Lop/R). These treatments can be further classified based on the use of adjunct antibiotics, which were prescribed depending on the patients' symptom severities and comorbidities. While South Korea has been relatively successful in managing the spread of the pandemic, the pharmacological management and treatment of its infected citizens have not been reported to date.

Although numerous clinical trials investigating various pharmacological agents as potential treatment of COVID-19 are under way, their results are not anticipated in the short-term, when they are needed the most. Herein, we present our experience on COVID-19 management with pharmacological therapy. This study aims to compare treatment responses of moderate COVID-19 patients who received HQ with antibiotics, Lop/R with antibiotics, or conservative treatment.

Methods

Study Population

A retrospective cohort study of 358 patients with laboratory-confirmed SARS-CoV-2 infection hospitalized in Korea Worker's Compensation & Welfare Service Daegu Hospital was conducted. All patients were diagnosed with COVID-19 by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) according to the WHO protocol[5]. Patients were admitted to the hospital from February 28, 2020, to April 28, 2020. They were stratified by severity according to National Institutes of Health (NIH) COVID-19 guidelines[6]. Individuals without shortness of breath, dyspnea, or abnormal imaging can be categorized as mild COVID-19; individuals who have evidence of lower respiratory disease by clinical assessment or imaging and oxygen saturation (SaO_2) >93% on room air at sea level can be categorized as moderate COVID-19; individuals who have respiratory frequency >30 breaths per minute, SaO_2 ≤93% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of

inspired oxygen (PaO_2/FiO_2) <300, or lung infiltrates >50% can be categorized as severe COVID-19 [6].

Of 358 COVID-19 patients, 270 patients remained for full analysis after excluding patients who did not adhere to treatment protocols and those with severe symptoms as they were referred to tertiary hospitals for intensive care at an early stage of the management. The ethics committee of Pusan National University Yangsan Hospital approved this study and granted a waiver of informed consent from study participants.

Procedures

The authors reviewed the electronic medical records of included patients and collected epidemiological, clinical, historical, laboratory, and treatment outcomes data. Patient confidentiality was protected by deidentifying patient information. The electronic data was also stored in a locked, password-protected computer. All but 3 patients were discharged from within the follow-up period up to April 28, 2020.

To identify SARS-CoV-2 infection, nasal swab samples were obtained from all patients on admission. The interval time between each follow-up specimen collection was 1.6 days in median. Collected swab samples were tested for SARS-CoV-2 using RT-PCR, and complete viral clearance was affirmed by two consecutive negatives on RT-PCR, which was defined by cycle threshold (Ct) value ≥40. Probable viral clearance was assigned to patients with Ct value ≥35. Additionally, patients received routine blood and biochemical tests; and for those with radiologic bronchiolitis/pneumonia findings, chest x-rays (CXR) or computed tomography (CT) were taken on a regular basis until lesions were resolved. All CXR and CT images were reviewed by experienced radiologists. The highest level of oxygen support each patient received during their hospitalization was also recorded. Fever was recorded if a patient's body temperature arose to 37.5 °C or higher, and information regarding all other COVID-19-related symptoms (cough, chill, myalgia, sputum, dyspnea, nasal discharge, and sore throat) was collected daily through a telephone survey using pre-specified questionnaires.

Patients in the HQ group received 200mg HQ tablets twice daily, and patients in the Lop/R group received lopinavir 200mg/ritonavir 50mg tablets twice daily. Azithromycin, when indicated, was used for 3 days in each patient and given as 500mg tablets once daily. Cefixime, when indicated, was used until remission of pneumonia and was administered as 100mg tablets twice daily.

Outcomes

Time from treatment initiation to 1) complete viral clearance (i.e. two consecutive negatives on PCR signified by Ct value ≥ 40), 2) probable viral clearance (Ct value ≥ 35), 3) discharge, and 4) symptom resolution were evaluated.

Statistical Analysis

Continuous variables were reported as mean (standard deviation [SD]), and categorial variables were reported as number (%). Categorical data were compared using the $\chi 2$ test or Fisher's exact test. Continuous variables were analyzed using Student's t-test or Mann-Whitney U test when comparing two groups and one-way ANOVA or Kruskal-Wallis test when comparing three groups. Kaplan-Meier curves were generated for primary endpoints and were tested with the log-rank test. Cox proportional hazard ratio (HR) models were used to determine HRs and 95% confidence intervals (CIs). All tests were 2-sided, and a *P* value less than 0.05 was considered statistically significant. All analyses were conducted using IBM SPSS, version 21.0 (SPSS Inc), or R software, version 3.6.0 (R Foundation for Statistical Computing).

Results

Baseline demographics and initial laboratory indices of patients

A total of 270 patients were included in this study (Table 1) and the enrollment of the study cohort is described in Figure 1. The mean age was 37.9 years (SD 15.1), and 174 (64.4%) were female. Interval time from symptom onset to PCR diagnosis was 5.6 days in average, and there was no significant difference between treatment groups (p = 0.524). The most commonly reported symptoms were cough (n= 144, [53.3%]), fever (n = 139 [51.7%]), and dyspnea (n = 53, [19.6%]). Fifty-nine patients had comorbidities, including hypertension (n = 27, [10%]), diabetes (n = 11, [4.1%]), dyslipidemia (n = 12, [4.4%]), and thyroid disease (n= 9, [3.3%]). A total of 60 (22.3%) patients had pneumonic lesions on CXR. Initial laboratory indices measured in patients include white blood cell count (5.8 $\times 10^3/\mu L$ [SD 1.5]), lymphocytes count (1.9 $\times 10^3/\mu L$ [SD 0.5]), LDH (226.5 U/L [SD 83.2]), creatinine (0.8 mg/dL [SD 0.2]), and C-reactive protein (0.3 mg/dL [SD 0.6]).

Of the 270 mild and moderate COVID-19 patients, moderate COVID-19 patients who have dyspnea or pneumonia lesions were further categorized into three different groups: those treated with Lop/R plus antibiotics (n = 35), those treated with HQ plus antibiotics (n = 22), and those given only conservative treatment (n= 40) (Table 2). All patients received standard conservative management. Baseline characteristics of patients in HQ plus antibiotics group and Lop/R plus antibiotics group were generally similar except for level of creatinine, glucose, and prothrombin time (international normalized ratio). However, patients who received conservative care showed less lesions on CXR compared to the patients who received HQ plus antibiotics or Lop/R plus antibiotics, suggesting a milder clinical picture in these patients (Table 2).

General clinical outcomes

There were significant differences between the three treatment groups in the following outcome

variables: length of time to complete viral clearance, length of time to cycle threshold (Ct) value above 35, and length of time to resolution of fever and cough symptoms (Table 3). HQ plus antibiotics group demonstrated the shortest length of time to all of the aforementioned endpoints. Patients in the conservative management group experienced less adverse effects compared to patients in active drug groups, and there were no significant differences in mortality rates or rate of referral to tertiary hospitals or ICUs between all treatment groups (Table 3).

Among the outcome variables that were shown to be significantly different between the three groups, cough duration and adverse effects of treatment (total) did not show significant differences when Lop/R plus antibiotics group and HQ plus antibiotics group were directly compared ((6.8 days[SD 5.6] vs 4.1 days[SD 2.3], p = 0.284) and (12 [34.3%]vs 7 [31.8%], p = 0.847)). Commonly observed adverse effects were increased AST/ALT (9 cases out of 97), nausea/vomiting (6 cases out of 97). Table 3 portrays these clinical outcome comparisons, and the key clinical outcomes such as time to viral clearance and time to resolution of cough symptoms were demonstrated using Kaplan-Meier curves.

Natural course of mild and moderate COVID-19

The time to viral clearance were compared between mild and moderate COIVD-19 patients who received standard supportive management using Kaplan-Meier curves. Significantly shorter duration to viral clearance was observed in mild COVID-19 compared to moderate COVID-19 (log-rank p = 0.012, Figure 2A).

Treatment response.

The length of time to viral clearance, which was indicated by negative conversion on PCR after initiation of treatment, was significantly shorter with HQ plus antibiotics than with Lop/R plus antibiotics (HR, 0.49; 95% CI, 0.28 to 0.87) or with conservative treatments (HR, 0.44; 95% CI, 0.25 to 0.78). However, there was no significant difference between groups that received Lop/R plus antibiotics and conservative treatment (log-rank p = 0.658, Figure 2B).

Hospital stay from initiation of treatment to discharge was also significantly shorter with HQ plus antibiotics than with Lop/R plus antibiotics (HR, 0.53; 95% CI, 0.30 to 0.93) or with conservative management alone (HR, 0.49; 95% CI, 0.28 to 0.87). However, there was no significant difference between groups that received Lop/R plus antibiotics and conservative treatment (log-rank p = 0.757, Figure 2C). The treatment responses of the patients in each of the three treatment groups are depicted in a bar-plot format in Figure 4.

The adjunct use of antibiotics

Subgroup analysis was performed between patients who received Lop/R alone and patients who received Lop/R plus antibiotics. The length of the time to viral clearance after treatment

initiation was significantly shorter in patients who received both Lop/R and antibiotics (HR 0.81, 95% CI, 0.70 to 0.93, Figure 3).

Discussion

The present study is the first report on pharmacological management of COVID-19 from South Korea. This retrospective cohort study compared treatment responses to three different treatment protocols in moderate COVID-19 patients who experienced dyspnea and/or mild pneumonia using several clinical outcome measures. HQ plus antibiotics showed better, quicker clinical improvement compared to Lop/R plus antibiotics and conservative treatment group in terms of viral clearance, hospital stay, and symptom(cough) resolution. The effect of Lop/R with antibiotics was not shown to be superior to conservative treatment. Our additional subgroup analysis compared Lop/R plus antibiotics and Lop/R alone, and earlier viral clearance after treatment initiation was observed with the adjunct antibiotics use.

We classified severity of COVID-19 according to National Institutes of Health (NIH) guidelines [6] and identified that there is a difference in the natural courses between mild and moderate COVID-19 in terms of viral clearance (Figure 2A). Mild patients experience a shorter duration from diagnosis to PCR-negative conversion compared to moderate patients. While many studies have reported on the differences between severe and non-severe COVID-19 [7-9], there is limited evidence on the differences between mild and moderate cases; our results provide a rationale to distinguish these patient groups for individualized treatment and triage purposes.

For moderate COVID-19 patients who require hospitalization according to the guideline[6], HQ plus antibiotics achieved fastest viral clearance and discharge of the three treatment methods (Figure 2B,C). It is notable that HQ plus antibiotics group had better clinical outcomes than the conservative treatment group despite the worse baseline clinical profiles (i.e. more lesions seen on initial CXR) and prognostic factors such as age, LDH, lymphocyte count, and CRP [10] (Table 2). Our results are in accordance with several in-vitro studies showing effectiveness of HQ against SARS-CoV-2 [11-13] and various clinical trials associated with the use of HQ with or without the adjunct use of azithromycin. RCTs have shown significant reduction in viral-load[14], earlier time to symptom resolution [15], and improvement in chest radiographs [15]. However, there is also evidence to the contrary as Tang et al. reported no differences in negative conversion rate [16] in patients treated with HQ compared to standard supportive treatment; thus more data must be accrued to draw definitive conclusions, and clinicians must be mindful that evidence for treatment of COVID-19 is still far from concrete.

Recent study by Geleris et al. that analyzed 1376 patients concluded no beneficial effect of HQ on patients' mortality and progression to severe disease [17]. It should be noted that primary endpoints and population of our study differ from that of Geleris et al.; we mainly focused on viral clearance and symptom duration in moderate patients, whereas the study by Geleris et al.

focused mostly on mortality and intubation rates in severe cases. Although reducing mortality and intubation rate in severe cases is clinically important, expediting viral clearance in moderate COVID-19 patients are as much relevant for immediate application in many areas around the world, and several RCTs have been conducted in this regard [14, 18, 19]. Shortened viral clearance enables earlier discharge and subsequently reduces medical cost for hospitalization and promotes effective allocation of limited medical resources. In addition, while still inconclusive, many of experts view positive viral loads as a potential risk of the spread of the virus[7, 20, 21], and in this respect expedited viral clearance may reduce risk of transmission and subsequently reduce the total burden of COVID-19 on a population's healthcare system.

Azithromycin and cefixime were prescribed together with either HQ or Lop/R in our study cohort for management of pneumonia and bacterial co-infection as per recommendations from the Korean Society of Infectious Disease[22] and other literatures[23-27]. In our subgroup analysis, Lop/R plus antibiotics showed earlier viral clearance after treatment initiation compared to Lop/R alone (Figure 3). While no strong consensus or evidences support the adjunct use of antibiotics for COVID-19, there is empirical evidence that azithromycin added to HQ led to superior viral clearance compare to HQ alone [14]. The underlying mechanism of antibiotics' effect on COVID-19 is uncertain, but the immunomodulatory function of reducing production of inflammatory cytokines including Interleukin-6 and TNF-alpha [28] by azithromycin is a possible explanation.

In our cohort, no mortality or serious adverse effects were observed. A total of 20 cases of minor adverse reactions to treatment were reported (20 out of 97 cases). Commonly reported adverse reactions were increased AST/ALT, nausea and vomiting, and abdominal symptoms. However, all patients with adverse reactions were discharged without any harmful sequelae. AST/ALT returned to normal before discharge in all patients except one, but this particular patient had elevated AST/ALT at baseline. The absence of serious adverse events may be attributable to our protocol, which prescribed reduced dosages of medications administered at once (i.e. 200mg HQ tablet per each) by using a twice daily regimen.

We presented treatment response for each treatment protocol, visualized using bar plots (Figure 4). Our results suggest that the time gap between symptom termination and viral clearance (i.e. time to negative conversion in PCR) is substantial, with long asymptomatic periods before discharge. A previous study from China, which analyzed 55 COVID-19 patients showed a similar pattern in mild patients [29]. This finding may indicate that immune systems of non-severe COVID-19 patients do not aggressively respond to the virus while it is still in their body systems. This is different from the course of severe COVID-19 patients who generally experience shorter time gaps between symptom termination and viral clearance, with relatively short asymptomatic periods before discharge [29, 30]. This distinction possibly stems from increased immune/inflammatory reaction to the virus in severe COVID-19. Altogether, the immune response of each individual is deemed an important underlying driver of COVID-19 disease course. This hypothesis may explain our result that HQ (immunomodulatory agent) and

azithromycin (antibacterial and immunomodulatory agents) showed better clinical outcomes for moderate COVID-19 than the antiviral agent Lop/R. However, this hypothesis remains speculative and warrants further research.

Although not supported in this study, antiviral agents are still a potential treatment modality for COVID-19. In our opinion, the timing of antiviral intervention may be crucial to achieve the full benefit of these agents. Considering the results from previous studies on Lop/R [18, 31, 32], antiviral agents may work best on patients at the early peak of viral replication and active shedding; the effect of antivirals may fade as patients proceed to a more advanced disease status. This could potentially explain the heterogeneity of results on Lop/R. Further trials taking this variable into account are needed to elucidate efficacy trajectories of antiviral agents on different initiation timings.

Limitations

Our study has several limitations. Although confounding factors and bias was corrected using various statistical methods and by setting up detailed definitions, there can be uncontrolled factors and bias due to the retrospective study design. Secondly, QT prolongation or retinopathy, known adverse effects of hydroxychloroquine, were not measured in our study ; while this must be kept into account as in any patient receiving hydroxychloroquine, no serious adverse reactions including cardiac toxicity or retinopathy were observed in our study population. Only one patient in HQ plus antibiotics group experienced tachycardia which was resolved shortly. Lastly, the baseline characteristics of our treatment subgroups are heterogeneous (Table 2). While Lop/R and HQ groups are almost identical and well-controlled, the conservative treatment group was composed of slightly milder patients. However, such differences in baseline has not substantially affected the interpretation of our results as patients in HQ plus antibiotics group showed better outcomes than patients in conservative management group, albeit having worse prognostic factors including age, LDH, WBC count, lymphocyte count, and CRP.

Conclusions

HQ with antibiotics was associated with better clinical outcomes in terms of time to viral clearance, and resolution of cough symptoms compared to Lop/R with antibiotics or conservative treatment. The effect of Lop/R with antibiotics was not superior to conservative management alone. The adjunct use of the azithromycin and cefixime might provide additional benefit to COVID-19 management but warrants further evaluation.

List of abbreviations

COVID-19: Coronavirus disease 2019
HQ: Hydroxychloroquine
Lop/R: Lopinavir-ritonavir

RT-PCT: Real-time polymerase chain reaction
Ct value: Cycle threshold value
CXR: Chest X-ray
CT: Computed tomography
HR: Hazard ratio
SD: Standard deviation
CI: Confidence interval

Declarations

Ethics approval and consent to participate

The ethics committee of Pusan National University Yangsan Hospital approved this study an d granted a waiver of informed consent from study participants.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no competing interests to disclose

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Author's contributions

MSK, SWJ, MHA, YKP, BOK, HWP, WY, JJ collected and analyzed the data.

MSK, MHA wrote the initial draft of the manuscript, synthesizing the information and ideas collected

WJK helped complete the manuscript.

MSK produced the images included in the manuscript

THH, SHK oversaw the entire investigation and contributed intellectual information crucial for the completion of this manuscript

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Table 1. Demographic characteristics and initial laboratory indices of mild and moderate COVID-19 patients

	Overall COVID-19 patients	Mild COVID-19 patients	Moderate COVID-19 patients	p value* (mild versus moderate COVID-19)
Number of patients	270	173	97	
Age, years	37.9 (15.1)	35.5 (14.6)	42.2 (15.3)	<0.001
Sex, female	174 (64.4)	95 (54.9)	79 (81.4)	<0.001
BMI, kg/m^2	23.1 (3.5)	23.2 (3.6)	23.0 (3.4)	0.637
Lesion on CXR	60 (22.3)	0 (0)	60 (62.5)	<0.001
Comorbidities				
Hypertension	27 (10.0)	16 (9.2)	11 (11.3)	0.583
Diabetes mellitus	11 (4.1)	9 (5.2)	2 (2.1)	0.337
Dyslipidemia	12 (4.4)	7 (4.0)	5 (5.2)	0.761
Thyroid	9 (3.3)	5 (2.9)	4 (4.2)	0.725
Symptoms				
Fever (>37.5℃)	139 (51.7)	71 (41.3)	68 (70.1)	<0.001
Chill	47 (17.4)	24 (13.9)	23 (23.7)	0.041
Myalgia	62 (23.0)	24 (13.9)	38 (39.2)	<0.001
Cough	144 (53.3)	76 (43.9)	68 (70.1)	<0.001
Dyspnea	53 (19.6)	0 (0)	53 (54.6)	<0.001
Sputum	125 (46.3)	67 (38.7)	58 (59.8)	0.001
Nasal discharge	124 (45.9)	70 (40.5)	54 (55.7)	0.016
Sore throat	99 (36.7)	56 (32.4)	43 (44.3)	0.050
Asymptomatic patients	52 (19.3)	46 (26.6)	6 (6.2)	<0.001
Vital signs				
Systolic blood pressure, mmHg	127.4 (16.1)	128.5 (13.8)	125.5 (19.4)	0.202
Diastolic blood pressure, mmHg	77.2 (10.9)	77.4 (10.2)	76.7 (12.1)	0.656
Heart rate, per min	86.6 (12.0)	87.3 (12.5)	85.4 (11.1)	0.229
Respiratory rate, per min	19.9 (0.5)	20.0 (0.3)	19.9 (0.8)	0.811
Body temperature, ℃	37.0 (0.4)	37.0 (0.4)	37.0 (0.5)	0.839
Initial laboratory indices				
White blood cells, ×10^3/μL	5.8 (1.5)	6.0 (1.6)	5.5 (1.3)	0.015
Lymphocytes, ×10^3/μL	1.9 (0.5)	2.0 (0.5)	1.8 (0.5)	0.024
Red blood cells, ×10^6/μL	4.6 (0.5)	4.7 (0.5)	4.5 (0.5)	0.001
Hemoglobin, g/dL	13.8 (1.6)	14.0 (1.7)	13.5 (1.4)	0.007
Hematocrit, %	41.7 (4.2)	42.3 (4.4)	40.7 (3.6)	0.002
Platelet, ×10^3/μL	266.5 (64.4)	270.0 (62.6)	260.4 (67.2)	0.260
Total bilirubin, mmol/L	0.6 (0.3)	0.6 (0.3)	0.6 (0.4)	0.348
AST, U/L	24.7 (19.7)	25.2 (22.0)	23.9 (14.9)	0.609
ALT, U/L	25.2 (21.9)	26.7 (21.2)	22.5 (22.9)	0.145
LDH, U/L	226.5 (83.2)	225.0 (85.5)	229.2 (79.2)	0.705
Albumin, g/dL	4.3 (0.3)	4.4 (0.3)	4.2 (0.3)	<0.001
BUN, mg/dL	12.2 (3.3)	12.3 (3.3)	12.1 (3.3)	0.742
Creatinine, mg/dL	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.031
Glucose, mg/dL	96.3 (44.6)	96.0 (45.2)	96.8 (43.9)	0.885
Triglyceride, mg/dL	158.5 (72.0)	163.6 (71.9)	149.5 (71.7)	0.137
HDL, mg/dL	46.1 (11.9)	46.9 (13.2)	44.7 (9.1)	0.121
Total cholesterol, mg/dL	162.5 (32.3)	162.1 (32.3)	163.2 (32.6)	0.797
PT (INR), %	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	0.532
CRP, mg/dL	0.3 (0.6)	0.2 (0.3)	0.5 (0.9)	0.003

Expressed as mean (standard deviation) for continuous variables and number count (percentage) for categorical variables; *p value for mild COVID-19 versus moderate COVID-19, continuous variables are analyzed by student t-test or Mann-Whitney U test and categorical variables are analyzed by Chi-square test or Fisher's exact test; AST: Aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; BUN: blood urea nitrogen; HDL: high-density lipoproteins; PT (INR): prothrombin time (international normalized ratio); CRP: c-reactive protein

Table 2. Demographic characteristics and initial laboratory indices of moderate COVID-19 patients in each treatment group

	Moderate COVID				
	Lopinavir-Ritonavir + antibiotics†	Hydroxy-chloroquine + antibiotics†	Conservative treatment	p value‡ (L-R versus HQ)	p value* (between all treatment groups)
Number of patients	35	22	40		
Age, years	49 (13.9)	42.5 (15.1)	36.1 (14.3)	0.102	0.001
Sex, female	25 (71.4)	21 (95.5)	33 (82.5)	0.027	0.074
BMI, kg/m^2	23.9 (4.1)	22.6 (3.2)	22.4 (2.6)	0.213	0.363
Lesions on CXR	32 (91.4)	21 (95.5)	7 (17.9)	0.566	<0.001
Interval time from symptom onset to PCR diagnosis, days	5.5 (4.6)	6.1 (5.1)	4.6 (2.9)	0.701	0.524
Comorbidities					
Hypertension	5 (14.3)	1 (4.5)	5 (12.5)	0.248	0.609
Diabetes mellitus	1 (2.9)	1 (4.5)	0 (0)	0.738	0.383
Dyslipidemia	2 (5.7)	1 (4.5)	2 (5.0)	0.849	0.997
Thyroid	0 (0)	2 (9.1)	2 (5.1)	0.072	0.891
Symptoms					
Fever (>37.5℃)	21 (60)	16 (72.7)	31 (77.5)	0.327	0.244
Chill	8 (22.9)	7 (31.8)	8 (20.0)	0.454	0.572
Myalgia	15 (42.9)	7 (31.8)	16 (40.0)	0.405	0.701
Cough	27 (77.1)	16 (72.7)	25 (62.5)	0.706	0.367
Dyspnea	11 (31.4)	9 (40.9)	33 (82.5)	0.465	<0.001
Sputum	19 (54.3)	15 (68.2)	24 (60.0)	0.298	0.581
Nasal discharge	19 (54.3)	13 (59.1)	22 (55.0)	0.722	0.933
Sore throat	12 (34.3)	8 (36.4)	23 (57.5)	0.873	0.090
Asymptomatic patients	3 (8.6)	1 (4.5)	2 (5.0)	0.566	0.878
Vital signs					
Systolic blood pressure, mmHg	126.0 (16.0)	126.0 (15.0)	124.9 (24.4)	0.995	0.560
Diastolic blood pressure, mmHg	75.5 (12.5)	77.6 (12.9)	77.4 (11.5)	0.550	0.825
Heart rate, per min	84.8 (10.6)	86.2 (12.6)	85.5 (10.9)	0.643	0.651
Respiratory rate, per min	20.0 (0.0)	20.0 (0.0)	19.8 (1.3)	1.000	0.755
Body temperature, ℃	37.0 (0.5)	37.0 (0.4)	36.9 (0.5)	0.847	0.267
Initial laboratory indices					
White blood cells, $\times10^3/\mu L$	5.5 (1.5)	5.1 (1.2)	5.8 (1.2)	0.335	0.032
Lymphocytes, $\times10^3/\mu L$	1.8 (0.5)	1.7 (0.4)	2.1 (0.5)	0.454	0.002
Red blood cells, $\times10^6/\mu L$	4.5 (0.4)	4.4 (0.4)	4.6 (0.5)	0.501	0.003
Hemoglobin, g/dL	13.6 (1.1)	13.1 (1.1)	13.6 (1.8)	0.101	0.009
Hematocrit, %	41.0 (2.9)	40.0 (3.0)	40.8 (4.5)	0.138	0.006
Platelet, $\times10^3/\mu L$	261.8 (86.3)	257.5 (54.3)	260.8 (54.6)	0.842	0.681
Total bilirubin, mmol/L	0.7 (0.4)	0.6 (0.6)	0.5 (0.3)	0.452	0.073
AST, U/L	26.8 (17.6)	22.5 (8.0)	21.9 (15.2)	0.229	0.698
ALT, U/L	24.2 (22.7)	19.3 (12.2)	22.8 (28.0)	0.379	0.433
LDH, U/L	239.2 (61.2)	258.7 (130.3)	202.8 (39.2)	0.527	0.010
Albumin, g/dL	4.0 (0.3)	4.1 (0.3)	4.4 (0.3)	0.331	<0.001
BUN, mg/dL	12.3 (3.4)	11.6 (3.5)	12.2 (3.0)	0.449	0.839
Creatinine, mg/dL	0.8 (0.2)	0.7 (0.1)	0.7 (0.1)	0.030	0.001
Glucose, mg/dL	118.3 (59.0)	88 (24.5)	82.4 (26.0)	0.012	0.007
Triglyceride, mg/dL	142.0 (65.4)	149.0 (53.0)	156.5 (86.0)	0.678	0.406

HDL, mg/dL	43.0 (9.3)	46.0 (10.3)	45.4 (8.2)	0.255	0.258
Total cholesterol, mg/dL	165.2 (36.5)	158.9 (23.8)	163.9 (33.7)	0.483	0.899
PT (INR), %	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	0.022	0.050
CRP, mg/dL	0.8 (1.1)	0.6 (1.2)	0.1 (0.1)	0.669	0.004

Expressed as mean (standard deviation) for continuous variables and number count (percentage) for categorical variables; ‡p value for Lopinavir-Ritonavir (L-R) plus antibiotics versus Hydroxychloroquine (HQ) plus antibiotics, continuous variables are analyzed by student t-test or Mann-Whitney U test and categorical variables are analyzed by Chi-square test or Fisher's exact test; *p value for L-R plus antibiotics versus HQ plus antibiotics versus conservative treatment, continuous variables are analyzed by one-way ANOVA or Kruskal-Wallis test and categorical variables are analyzed by Chi-square test or Fisher's exact test; †Antibiotics; antibiotics include azithromycin and cefixime; AST: Aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; BUN: blood urea nitrogen; HDL: high-density lipoproteins; PT (INR): prothrombin time (international normalized ratio); CRP: c-reactive protein

Table 3. Outcomes of moderate COVID-19 patients in each treatment group

	Lopinavir–Ritonavir + antibiotics†	Hydroxy-chloroquine + antibiotics†	Conservative treatment	p value* (L-R vs. HQ)	p value‡ (between three treatment groups)
Number of patients	35	22	40		
Hospital stay after initiation of treatment, days	19.9 (5.8)	16.5 (4.0)	20.7 (7.8)	0.025	0.063
time from treatment initiation to viral clearance, days	19.1 (5.7)	15.3 (3.8)	20.7 (10.3)	0.011	0.011
time from treatment initiation to Ct value > 35, days	15.4 (2.9)	12.6 (2.5)	14.5 (3.1)	0.001	0.005
Required O_2 supply	0 (0)	0 (0)	0 (0)	1.000	1.000
Refer to tertiary hospital/ICU	4 (11.4)	1 (4.5)	0 (0)	0.375	0.189
Mortality	0 (0)	0 (0)	0 (0)	1.000	1.000
Symptom duration after initiation of treatment, days					
Fever (>37.5℃)	6.0 (4.7)	1.4 (0.5)	2.0 (2.4)	0.016	0.024
Chill	1.3 (0.5)	1.0 (0.0)	1.6 (1.1)	0.629	0.603
Myalgia	5.8 (5.2)	3.8 (1.9)	2.9 (2.7)	0.710	0.242
Cough	6.8 (5.6)	4.1 (2.3)	8.9 (7.6)	0.284	0.010
Dyspnea	3.7 (4.7)	4.0 (3.3)	2.9 (2.8)	0.497	0.582
Sputum	5.2 (4.3)	5.1 (3.6)	7.6 (7.8)	0.890	0.787
Nasal discharge	3.8 (4.6)	2.8 (3.1)	4.3 (4.4)	0.525	0.499
Sore throat	6.0 (6.2)	3.3 (4.1)	4.2 (3.9)	0.328	0.541
Azithromycin use, days	4.2 (1.3)	3.4 (1.9)	-	0.058	-
Cefixime use, days	8.9 (2.5)	8.7 (2.3)	-	0.720	-
Lopinavir–Ritonavir or Hydroxy-chloroquine use, days	8.3 (2.8)	8.9 (2.1)	-	0.364	-
Adverse effects of treatment, total	12 (34.3)	7 (31.8)	1 (2.5)	0.847	0.001
Nausea/vomiting	4 (11.4)	2 (9.1)	0 (0)	0.781	0.066
Abdominal discomfort/diarrhea	3 (8.6)	1 (4.5)	0 (0)	0.566	0.243
Tachycardia	0 (0)	1 (4.5)	0 (0)	0.207	0.227
Increased total bilirubin	0 (0)	1 (4.5)	0 (0)	0.207	0.227
Increased BUN	1 (2.9)	0 (0)	0 (0)	0.428	0.998
Increased AST/ALT	4 (11.4)	4 (18.2)	1 (2.5)	0.479	0.045
Serious adverse effects	0 (0)	0 (0)	0 (0)	1.000	1.000

Expressed as mean (standard deviation) for continuous variables and number count (percentage) for categorical variables; *p value for Lopinavir–Ritonavir plus antibiotics versus Hydroxychloroquine plus antibiotics, continuous variables are analyzed by student t-test or Mann-Whitney U test and categorical variables are analyzed by Chi-square test or Fisher's exact test; p value‡ for Lopinavir–Ritonavir plus antibiotics versus Hydroxychloroquine plus antibiotics versus conservative treatment, continuous variables are analyzed by one-way ANOVA or Kruskal-Wallis test and categorical variables are analyzed by Chi-square test or Fisher's exact test; †Antibiotics: antibiotics include azithromycin and cefixime; Ct value: cycle threshold value; BUN: blood urea nitrogen; AST: Aspartate aminotransferase; ALT: alanine aminotransferase

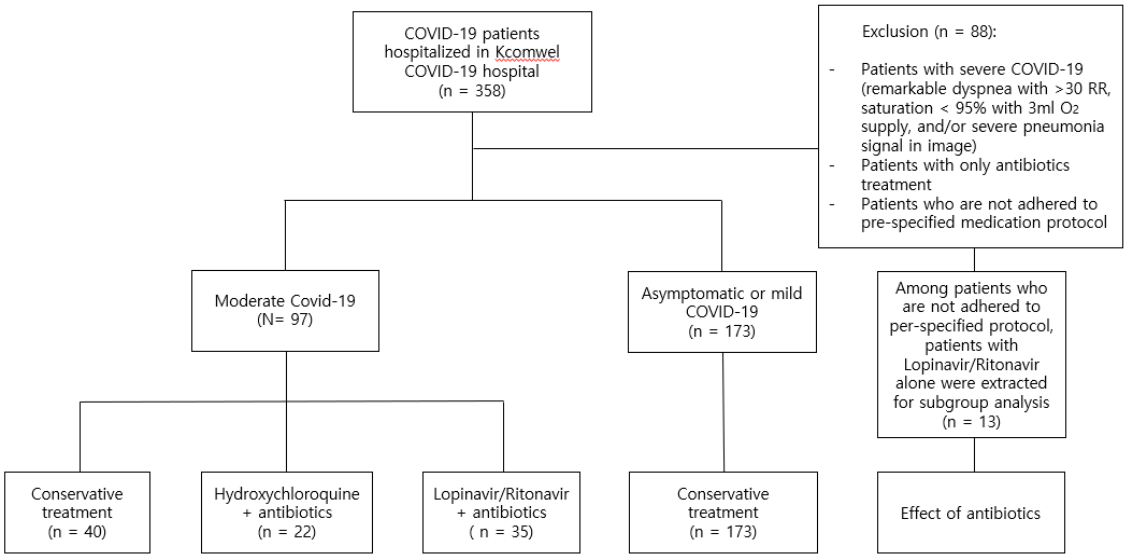
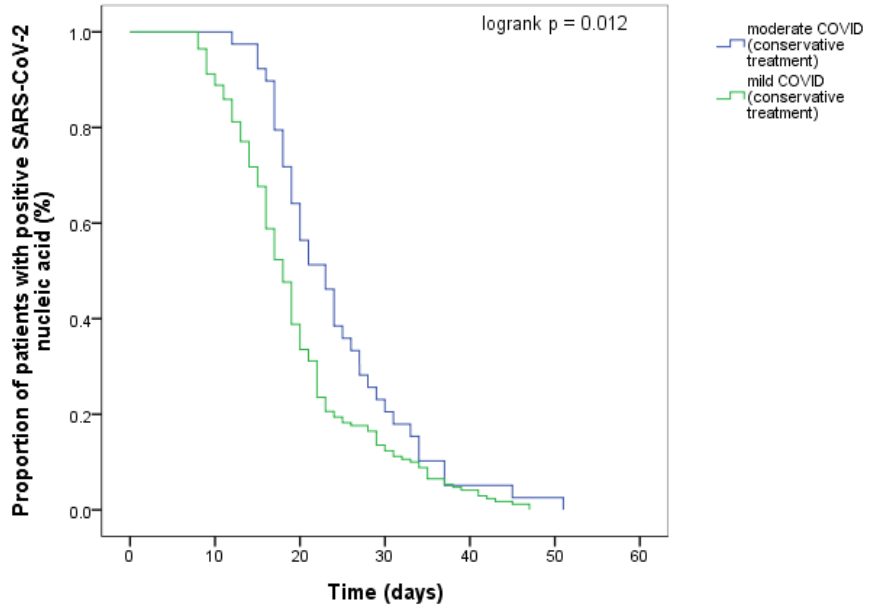
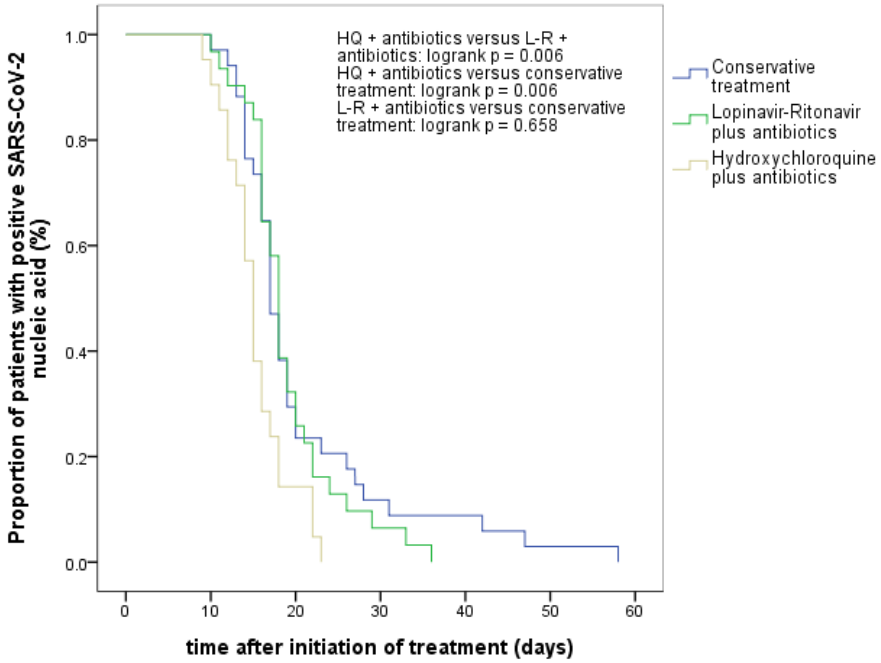


Figure 1. Flowchart for enrollment of the study cohort

A. Viral clearance of mild and moderate COVID-19 patients



B. Viral clearance of each treatment group of moderate COVID-19 patients



C. Hospital stay of each treatment group of moderate COVID-19 patients

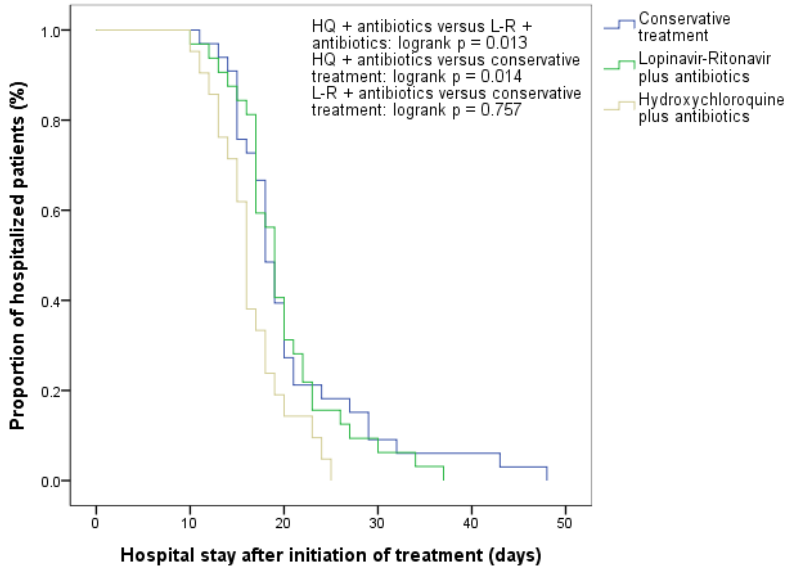


Figure 2. Kaplan-Meier survival curves for (A) time to viral clearance in patients with different severities (mild vs. moderate), (B) time to viral clearance, and (C) time to discharge in different treatment groups.

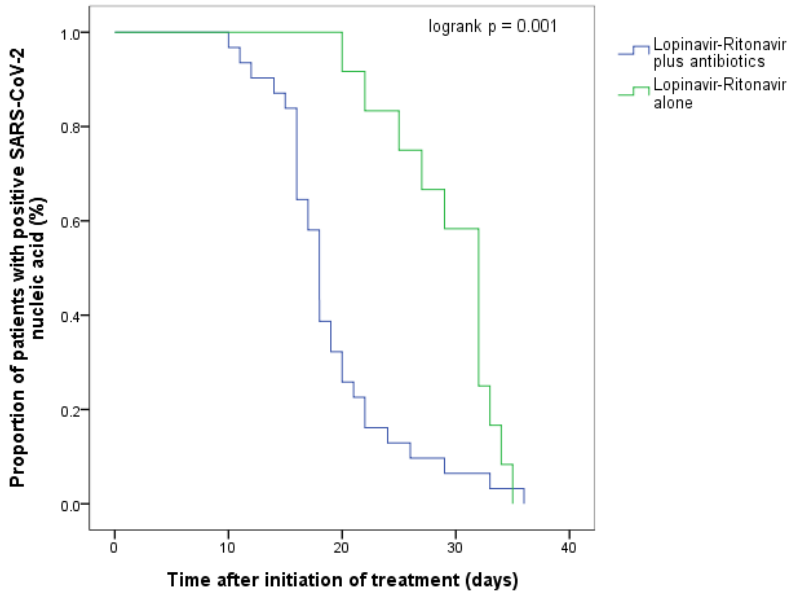
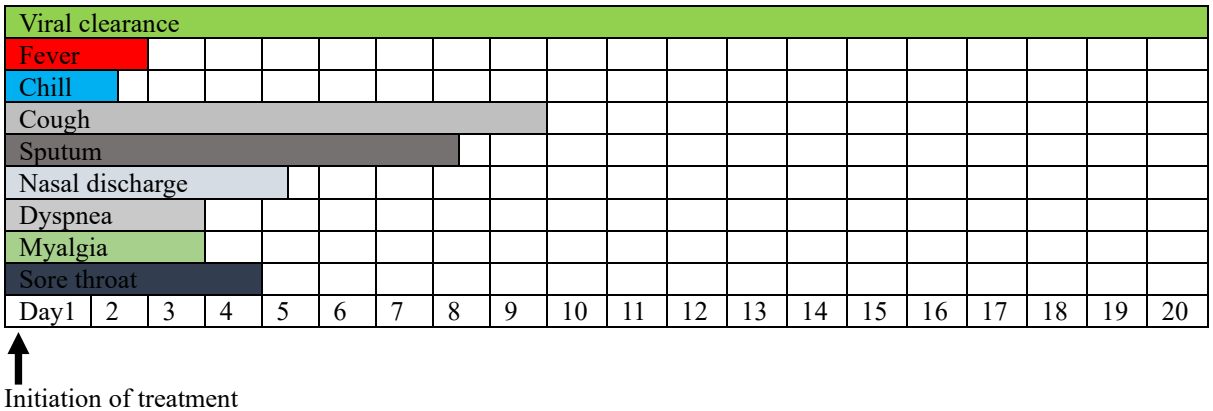
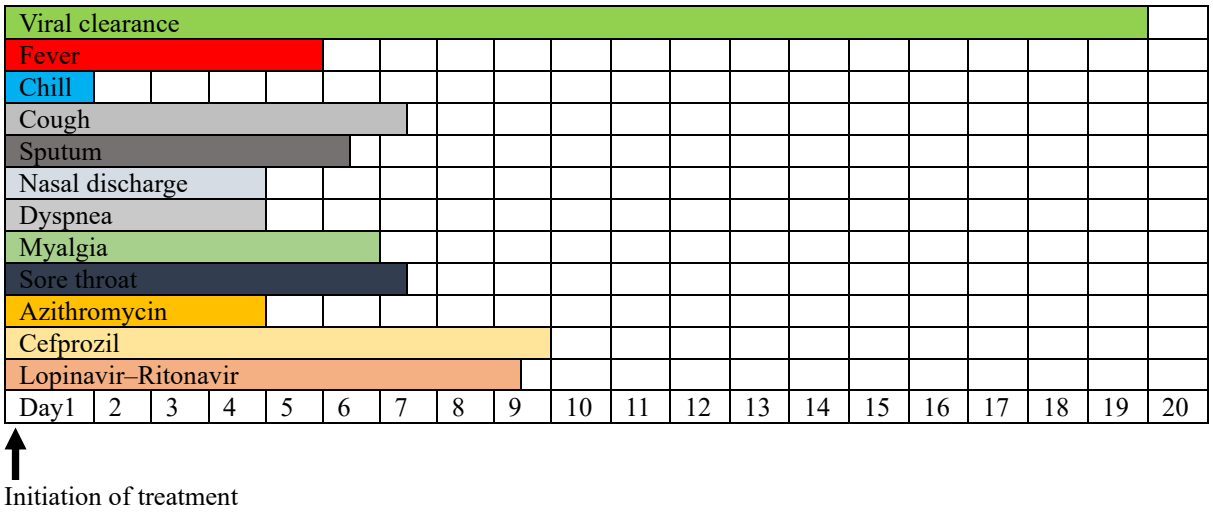


Figure 3. Subgroup analysis for the length of time until viral clearance with Lopinavir-Ritonavir alone versus Lopinavir-ritonavir plus antibiotics.

Conservative treatment



Lopinavir–Ritonavir



Hydroxychloroquine

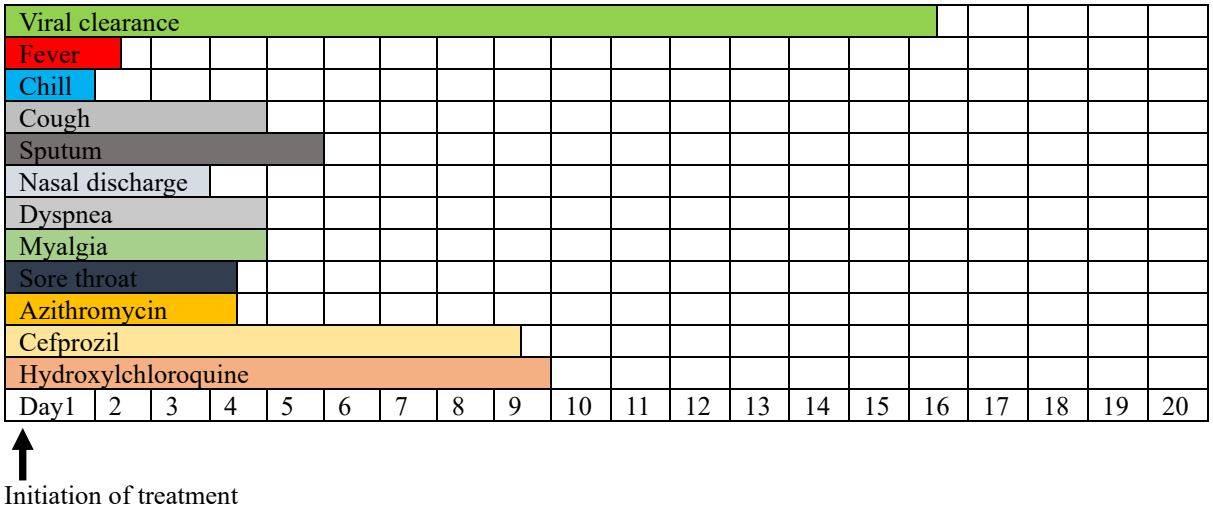


Figure 4. Treatment response of each drug group of moderate COVID-19 patients after initiation of treatment.