

Efficacy and Safety of Arbidol in Treatment of Patients with COVID-19 Infection: A Randomized Clinical Trial

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Research

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Abstract

Background: The outbreak of COVID-19 has led to a high demand for finding effective antiviral agents. Preliminary experiments showed that Umifenovir could inhibit coronavirus replication in vivo. There is limited data on the clinical efficacy of COVID-19-infected pneumonia. Therefore, we aimed to evaluate this medication based on clinical findings.

Methods: The present study was designed as a clinical trial to investigate the advantages and disadvantages of this medicine compared to empirical treatment. For this purpose, multi-stage sampling was considered. 56 people who have mild to moderate symptoms without signs of severe pneumonia, were selected by accidental non-random sampling method. This sample size was subsequently divided into two groups (group A treated with hydroxychloroquine and group B who treated with combination hydroxychloroquine and Umifenovir) by randomized block sampling (1:1). During the study, three patients left the case group. Their clinical signs and symptoms were evaluated on 3th and 7th and 14th days after onset of illness while taking these medicines in the disease course. The SPSS software was used for data analysis and the significance level was considered to be $P < 0.05$.

Results: On the seventh days after visit patients, there were statistically significant differences in recuperation dry cough ($p = 0.001$), weakness ($p = 0.004$), gastrointestinal symptoms ($p = 0.043$) and shortness of breath ($p = 0.001$) between the two groups, so that in patients who under prescription combination HCQ and Umifenovir group had a faster recovery. Generally during illness, there were statistically significantly faster amelioration myalgia ($p = 0.03$), gastrointestinal symptoms ($p = 0.047$), and weakness ($p = 0.007$) in patients who treated with both HCQ and Umifenovir.

Conclusion: Evaluation clinical findings in mild to moderate COVID-19 patients symptoms and signs recuperation faster in group who under prescription combination HCQ and Umifenovir regimen. In other words, adding Umifenovir to the empirical treatment accelerated the recovery process of patients' clinical symptoms.

Introduction

The COVID-19 was identified following the epidemic of the "unknown flu virus" that occurred in Wuhan, China (1). The incidence of infection is constantly increasing. The virus can easily be transmitted from one person to another (possibly even by asymptomatic patients) and is currently reported in all countries of the world. This has become a major public health problem (2, 3), with more than 10.5 million people infected (230,211 people in Iran) and more than 512,000 people died (10,958 in Iran) so far (4). The prevalence of infection has led to the empirical use of various antiviral therapies in infected patients (5). However, there still seems to be no treatment regimen with specific clinical efficacy and optimal effectiveness.

Umifenovir is a broad-spectrum antiviral drug that has been approved in several countries (6). The antiviral mechanism of this drug is mainly as follows: a) inhibition of the membrane fusion between viral

particles and plasma membranes, b) regulation of the immune response by producing interferons and activating macrophages, c) modulation of the expression of inflammatory cytokines such as interleukin-6, interleukin-8, and TNF α (6-8). Recent studies have also shown that Umifenovir has antiviral effects on other viruses such as herpes(9), Zika virus(10), and Ebola virus(11). In the laboratory, the efficacy of Umifenovir in inhibiting severe acute respiratory syndrome (SARS) coronavirus replication has been demonstrated(12, 13), and observational studies have reported the positive effect of this medication on the treatment of COVID-19(14, 15).

Umifenovir has been used as an anti-influenza drug in various countries for several decades(16, 17). In vitro studies have confirmed the antiviral effect of Umifenovir on coronavirus(12, 13, 16). The innate pathogenesis of the virus leads to mild symptoms in which antiviral therapy can quickly improve the primary symptoms. Then, increased cytokines in the lungs and bone marrow lead to worsening of symptoms of influenza virus or SARS-CoV infections(16, 18-20). Previous data have shown that there are two potential mechanisms involved in the process of lung damage caused by influenza virus, including viral pathogenesis and the host's innate immune responses to the disease(21).

Umifenovir inhibits the viral fusion with the host cell and stimulates the immune system and increases the phagocytic activity of macrophages through interferon production. This drug has a hepatic metabolism and is administered at a dose of 200 mg every 8 hours. The active ingredient of this drug is non-toxic and it rarely causes side effects.(16) Pruritus and skin rashes are among the rare side effects of this medicine and no other serious side effects have been reported. However, it is contraindicated in children under two years of age and pregnant and lactating women. Careful monitoring of its side effects should be done in patients with liver and kidney failures. The LD50 dose of this drug is 4 g/kg body weight(16). Therefore, due to the insufficient number of clinical trials and studies conducted on the treatment of this disease with this drug so far, as well as the lack of specific drug therapy, we aimed to examine the effects of this drug in a more detailed interventional study.

Methodology

Participants

This study is an open-label clinical trial conducted on patients with definitive diagnosis of COVID-19 (PCR testing from nasopharyngeal and oropharyngeal secretions or a clear view on the chest CT scan) (definitive evidence for SARS-CoV-2 in chest CT, Patchy Infiltration appearance and ground-glass opacities in lungs) who had referred to Imam Khomeini Hospital Complex, Tehran, Iran This study was conducted from April 20 to June 4, 2020. In this study, multi-stage sampling was considered. In the first stage, 56 people were selected by accidental non-random sampling method. This sample size was subsequently divided into two groups by randomized block sampling (with a randomized block design, the experimenter divides subjects into subgroups called blocks, such that the variability within blocks is less than the variability between blocks. Then, subjects within each block are randomly assigned to treatment conditions.) (1:1). During the study, three patients left the case group (two patients lost to

follow up, one patient discontinued intervention). These two groups included control (N=25) and case (N=28) arms. Their clinical symptoms were examined while taking these medicines in the disease course. (14-day follow-up for each patient). The inclusion criteria for the study were patients with age greater than or equal to 18 years, oral tolerance, and getting written informed consent from the patient and diagnosis of mild to moderate COVID-19 infection (Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) fatigue, anorexia, myalgias and Other non-specific symptoms, such as sore throat, nasal congestion, headache, diarrhoea, nausea and vomiting, have also been reported(1, 22-24) but should be without signs of severe pneumonia (including SpO₂ ≥ 90% on room air, respiratory rate > 30 breaths/min; severe respiratory distress) (25)). The exclusion criterion was the patient's basal Alanine aminotransferase (ALT) value greater than five times the normal range. (normal value for ALT in blood ranges from 29 to 33 units per liter (IU/L) for males and 19 to 25 IU/L for females)

The case group received hydroxychloroquine (HCQ) at a dose of 200 mg every 12 hours and Umifenovir at a dose of 200 mg every 8 hours for 10 days. The control group received the national treatment protocol proposed for COVID-19(26), including HCQ every 12 hours for 10 days and acetaminophen and Diphenhydramine oral syrup if needed.

With the exception of Umifenovir, all other standard interventions and treatments were the same for patients in both groups. Umifenovir was provided by the Center for Progress and Development (CPDI) of Iran Presidency and given to the infectious disease ward, and patients did not pay for it. Pharmstandard, one of the leading Russian pharmaceutical companies, is the manufacturer of this drug. Given the open-label nature of the trial, the department of pharmacotherapy was the research supervisor.

Measurements:

After obtaining written informed consent from the patients, demographic and clinical characteristics such as age, gender, BMI, history of underlying diseases including COPD, asthma, diabetes mellitus (DM), hypertension, malignancy, HIV, and taking immunosuppressive drugs were extracted and recorded from the patients' medical history.

In the beginning, factors such as fever, heart rate, respiratory rate, oxygen saturation, and tests such as white blood cell count (WBC), C-reactive protein (CRP), liver enzymes, bilirubin, Creatine phosphokinase(CPK), and electrolytes including sodium, magnesium, and potassium were recorded.

Clinical symptoms of patients with COVID-19 infection, such as nausea, vomiting, diarrhea, cough, shortness of breath, fever, body aches, loss of appetite, and other symptoms were also monitored, and changes in symptoms in terms of improvement or worsening were reported on the 3rd day after start treatment in each group as primary outcome, on the 7th day as secondary outcome, and on the 14th day as the final outcome.

The patients were also monitored for common side effects of Umifenovir, such as skin rashes and gastrointestinal symptoms such as nausea and vomiting, diarrhea or abdominal pain, jaundice, and bradycardia.

Ethical considerations

This study was approved by the Ethics Committee of Tehran University of Medical Sciences (TUMS) according to the 2013 Declaration of Helsinki. The written informed consent was obtained from all patients. The patients were informed that they could withdraw from the study at any time and continue their treatment according to the national protocol.

Statistical analysis

The Kolmogorov-Smirnov test was first used to assess whether the distribution of variables was normal. Continuous variables were expressed as median (interquartile range (IQR)) and their relationship was reported in the two groups using Mann-Whitney U test and Kruskal–Wallis test . Qualitative variables were expressed as numbers (percentages) and their relationship was analyzed using the Chi-square test and Fisher’s exact test. The Kaplan-Meier method was used to compare the improvement in disease symptoms during treatment between the two groups. The statistical analysis was performed using the SPSS software (version 25) and P-values<0.05 were considered statistically significant.

Results

Demographic and clinical characteristics

The statistical population included 53 patients with COVID-19 disease. Among these patients, 25 patients received hydroxychloroquine and 28 patients received a combination of HCQ and Umifenovir. All patients were in the mild to moderate group, and none of them had fever. There were no statistically significant differences in demographic variables such as age, gender, body mass index (BMI), primary symptoms, and patients’ lab tests between the two groups (*Tables 1, 2*).

Table 1. Demographic characteristics, symptoms and radiology findings in patients with Covid-19, Tehran, 2020

Variables	HCQ/Arbidol N (%)	HCQ N (%)	P-value
Gender			
Male	19(67.9)	13(52)	
Female	9(32.1)	12(48)	
Sleep disorders	4(14.3)	5(20)	0.42
Anosmia	2(7.1)	4(16)	0.28
Sore throat	13(46.4)	14(56)	0.48
Conjunctivitis	1(3.6)	0	0.53
Chest CT (Unilateral)	7(25)	12(48)	0.13
Chest CT (Bilateral)	16(57.1)	11(44)	0.13
Dry cough	24(85.7)	17(68)	0.12
Myalgia	27(96.4)	23(92)	0.46
Dyspnea	22(78.6)	11(44)	0.01
Gastrointestinal symptoms	8(28.6)	12(48)	0.14
Weakness	27(96.4)	25(100)	0.53
Chest pain	5(17.9)	12(48)	0.02

Table 2. Laboratory findings of patients with Covid-19, Tehran, 2020

Variables	HCQ/Arbidol (n=28) Median (IQR) , N (%)	HCQ (n=25) Median (IQR) ,N (%)	P-value
Age (yrs.)	46.5(36-57.5)	42(34-50.5)	0.533
BMI	25.05(23.75-25.6)	25.23(23.95-26.15)	0.06
Symptom duration before admission (day)	4(3-5)	4(3-5)	0.97
RR	22(21-23.75)	22(20-23)	0.351
PR	99.5(90.25-104.75)	91(86.5-100)	0.16
O2 saturation (%)	95(94.25-97)	96(95-97)	0.28
T (°C)	37.05(36.9-37.3)	37(36.9-37.5)	0.97
CRP (mg/L)	16.5(6.75-60)	14(7-29.5)	0.52
AST (IU/L)	27(18.25-36.25)	25(19.5-30)	0.22
ALT (IU/L)	27(18.25-36.25)	30(25.5-33)	0.21
Alk phosphatase (IU/L)	174(150-190.5)	202(170.5-233.5)	0.016
Cr (mg/dL)	0.95(0.825-1.1)	0.9(0.8-1.05)	0.31
Troponin (ng/L)	1.5(1.5-2.1)	1.5(1.5-1.5)	0.51
CPK (mg/dL)	100.5(66.5-156.5)	120(91.5-151)	0.57
Na (mEq/L)	140(139-141)	141(139-142)	0.15
K (mEq/L)	4.2(3.925-4.4)	4.1(4-4.2)	0.41
WBC (10 ³ /μl)	6.6 (5.2-7.652)	5.5 (4.85-6.55)	0.11
Lymphocytes (10 ³ /μl)	1.674(1.29-2.38)	1.53(1.281-1.874)	0.28
PLT (10 ³ /μl)	222(180.25-282)	215(199-246.5)	0.87
Need to hospitalization (yes)	1(3.6)	1(4)	0.98

Myalgia was the most common symptom at the onset of the disease, and most of the patients (94.3%) had myalgia upon entering into the study. However, there was no significant difference in the frequency of myalgia between the two groups (P = 0.46).

Treatment responses

On the third day of the disease, there were statistically significant differences in myalgia (p = 0.002), dry cough (p = 0.001), weakness (p=0.021), and gastrointestinal symptoms (p=0.001) between the two groups (*Table 3*) and the recovery rate was more in the Umifenovir group. On the seventh day, there were statistically significant differences in dry cough (p = 0.001), weakness (p = 0.004), gastrointestinal symptoms (p = 0.043), and shortness of breath (p = 0.001) between the two groups (*Table 3*) and the recovery rate was more in the Umifenovir group.

Table 3. Primary and secondary symptoms of patients with Covid-19, Tehran, 2020

Symptoms	HCQ/Arbidol N(%)	HCQ N(%)	P-Value
Myalgia 3 th day	2(7.1)	11(44)	0.002
7 th day	0(0)	1(4)	0.47
Dry cough 3 th day	21(75)	22(88)	0.001
7 th day	1(3.6)	17(68)	0.001
Chest pain 3 th day	3(10.7)	12(48)	0.003
7 th day	0(0)	5(20)	0.19
Weakness 3 th day	7(25)	14(56)	0.021
7 th day	2(7.1)	10(40)	0.004
Gastrointestinal symptoms 3 th day	0(0)	8(32)	0.001
7 th day	0(0)	4(16)	0.043
Dyspnea 3 th day	11(29.3)	16(64)	0.072
7 th day	2(7.1)	12(48)	0.001

In general, according to the Breslow (Generalized Wilcoxon) test and Kaplan-Maier curves (Figur 1,2,3) during the disease course, there were statistically significant differences in myalgia ($p = 0.03$), gastrointestinal symptoms ($p = 0.047$), and weakness ($p = 0.007$) between the two groups. However, there were no statistically significant differences in shortness of breath ($p = 0.29$) and dry cough ($P = 0.81$) between the two groups during the disease course.

Side effects

Umifenovir side effects include dermatitis, gastrointestinal symptoms (such as nausea and diarrhea), jaundice, and neurological symptoms assesst every three days but were not observed in any of the patients after 14 days.

Discussion

In this study, patients with mild to moderate disease symptoms (such as myalgia and fatigue) receiving Umifenovir in their treatment regimen recovered more quickly. Given the COVID-19 infection pandemic, there is an urgent need for an effective and specialized antiviral regimen to treat the clinical symptoms of the disease. To this end, due to the limited number of clinical trial studies, we decided to use a medicine that has had favorable primary outcomes in animals as well as case studies. Based on the results of the

present study, adding Umifenovir (due to its antiviral and anti-inflammatory effects) to empirical regimens accelerated the recovery process of patients' clinical symptoms.

In the current study, on the third day of the disease, there were statistically significant differences in myalgia, dry cough, weakness, and gastrointestinal symptoms between the two groups, and the recovery rate was better in the Umifenovir group. This means that primary symptoms were controlled in the patients by adding Umifenovir.

In addition to its antiviral mechanism, Umifenovir has potential immunomodulatory and anti-inflammatory effects on the expression of inflammatory cytokines. In vitro studies have shown that pro-inflammatory cytokines such as TNF- α , IL-8, and IL-6 decreased after treatment with Umifenovir(8). Acute respiratory distress syndrome (ARDS) caused by increased response to inflammatory cytokines/chemokine has also been shown to be one of the main mechanisms of SARS-CoV and MERS-CoV infections(16, 27). It seems that the effects of Umifenovir should be reflected in the secondary symptoms of the disease. In our study, on the seventh day, there were statistically significant differences in dry cough, weakness, gastrointestinal symptoms, and shortness of breath between the two groups, and the group receiving HCQ addition to Umifenovir had a faster recovery.

Another study reported an early improvement in radiological evidence of covid-19 infected pneumonia patients taking Umifenovir. This research also highlighted the antiviral and anti-inflammatory effects of this drug(8). However, another investigation claimed that Umifenovir had no positive effect on clinical and radiological improvement or even virus removal, and that the clinical efficacy of this drug differs from the severity of the disease(16).

Due to this inconsistency in results, the findings of present study demonstrated that gradually there were statistically significant differences in myalgia, gastrointestinal symptoms, and weakness between the case group (Umifenovir) and the control group. This means that with the use of Umifenovir, patients had significantly fewer symptoms over time, confirming that Umifenovir has antiviral and anti-inflammatory effects on this infection.

There were some limitations in this study. First of all, since there is no absolutely effective treatment for this disease, we used empirical treatment along with HCQ for the control group. Second, due to the high cost and a limited number of PCR test kits, we could not use this test to prove the disease and evaluate the response to treatment. Third, due to ethical considerations, the effect of Umifenovir was not assessed individually, so we added Umifenovir to the empirical treatment. Lastly, due to the limited sample size, we may not extrapolate the results to all the patients with Covid-19.

Conclusion

In this study, we concluded that the primary symptoms of patients with mild to moderate COVID-19 were controlled by adding Umifenovir to the empirical treatment. This drug had similar effects on secondary symptoms and in most cases, it reduced these symptoms. By using this method, patients significantly

recovered faster, confirming that Umifenovir could have antiviral and anti-inflammatory effects. It is also recommended that PCR testing and radiological response be added to patient evaluation in future studies.

Abbreviations

1.).
2. severe acute respiratory syndrome (SARS)
3. Alanine aminotransferase (ALT)
4. hydroxychloroquine (HCQ)
5. Center for Progress and Development of Iran (CPDI)
6. diabetes mellitus (DM)
7. white blood cell count (WBC)
8. C-reactive protein (CRP)
9. Creatine phosphokinase(CPK)
10. Tehran University of Medical Sciences (TUMS)
11. interquartile range (IQR)
12. body mass index (BMI)
13. Acute respiratory distress syndrome (ARDS)

Declarations

Ethics approval and consent to participate:

This study was approved by the Ethics Committee of Tehran University of Medical Sciences (TUMS) according to the 2013 Declaration of Helsinki (IR.TUMS.VCR.REC.1399.204). The written informed consent was obtained from all patients. The patients were informed that they could withdraw from the study at any time and continue their treatment according to the national protocol.

Availability of data and material:

Data could be available upon a reasonable request and with the permission of Tehran University of Medical Science ethical committee.

Competing interests:

The authors have no conflict of interest.

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Authors' contributions:

S.Ghaderkhani , A.Salami, A.salamikhaneshan, SA.AliNaghi contributed to the study conception and design, Data analysis and interpretation, and Critical revision of the article. A.Salami , A.salamikhaneshan, Pebrahimialavijeh, H.EmadiKouchak, H.khalili, Z.Ahmadinejad , M.Rasolinejad, M.Hajiabdolbaghi, S.Jafari, M.Hasannezhad, A.Seifi, L.abasian, f.ghiasvand, F.AlborziAvanaki. M.edalatifard and M.Rahimi conducted the interviews, collect the data and Data analysis. S.Ghaderkhani , A.Salami, wrote and revised the first draft. All authors read and approved the final manuscript.

Consent to publication:

Not applicable.

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Consent to publication:

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References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020;395(10223):497-506.
2. Mehraeen E, Behnezhad F, Salehi MA, Noori T, Harandi H, SeyedAlinaghi S. Olfactory and gustatory dysfunctions due to the coronavirus disease (COVID-19): a review of current evidence. *European Archives of Oto-Rhino-Laryngology*. 2020:1-6.
3. Asadollahi-Amin A, Hasibi M, Ghadimi F, Rezaei H, SeyedAlinaghi S. Lung involvement found on chest ct scan in a pre-symptomatic person with SARS-CoV-2 infection: a case report. *Tropical medicine and infectious disease*. 2020;5(2):56.
4. Organization WH. Novel Coronavirus (2019-nCoV): situation report 164. 2020.
5. Cao M, Zhang D, Wang Y, Lu Y, Zhu X, Li Y, et al. Clinical Features of Patients Infected with the 2019 Novel Coronavirus (COVID-19) in Shanghai, China. *medRxiv*. 2020.
6. Blaising J, Polyak SJ, Pecheur EI. Arbidol as a broad-spectrum antiviral: an update. *Antiviral research*. 2014;107:84-94.
7. Haviernik J, Stefanik M, Fojtikova M, Kali S, Tordo N, Rudolf I, et al. Arbidol (Umifenovir): A Broad-Spectrum Antiviral Drug That Inhibits Medically Important Arthropod-Borne Flaviviruses. *Viruses*. 2018;10(4).

8. Wang Y, Ding Y, Yang C, Li R, Du Q, Hao Y, et al. Inhibition of the infectivity and inflammatory response of influenza virus by Arbidol hydrochloride in vitro and in vivo (mice and ferret). *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*. 2017;91:393-401.
9. Du Q, Gu Z, Leneva I, Jiang H, Li R, Deng L, et al. The antiviral activity of arbidol hydrochloride against herpes simplex virus type II (HSV-2) in a mouse model of vaginitis. *International immunopharmacology*. 2019;68:58-67.
10. Fink SL, Vojtech L, Wagoner J, Slivinski NSJ, Jackson KJ, Wang R, et al. The Antiviral Drug Arbidol Inhibits Zika Virus. *Scientific reports*. 2018;8(1):8989.
11. Hulseberg CE, Feneant L, Szymanska-de Wijs KM, Kessler NP, Nelson EA, Shoemaker CJ, et al. Arbidol and Other Low-Molecular-Weight Drugs That Inhibit Lassa and Ebola Viruses. *Journal of virology*. 2019;93(8).
12. Kramarev SA, Moshchich AP. [The treatment of influenza and acute respiratory viral infections]. *Likars'ka sprava*. 2013(2):99-106.
13. Khamitov RA, Loginova S, Shchukina VN, Borisevich SV, Maksimov VA, Shuster AM. Antiviral activity of arbidol and its derivatives against the pathogen of severe acute respiratory syndrome in the cell cultures. *Voprosy virusologii*. 2008;53(4):9-13.
14. Wang Z, Chen X, Lu Y, Chen F, Zhang W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. *Bioscience trends*. 2020;14(1):64-8.
15. Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. *World journal of pediatrics : WJP*. 2020:1-9.
16. Xu K, Chen Y, Yuan J, Yi P, Ding C, Wu W. Clinical Efficacy of Arbidol in Patients with 2019 Novel Coronavirus-Infected Pneumonia: A Retrospective Cohort Study (2/12/2020). *The Lancet*. 2020.
17. Kadam RU, Wilson IA. Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. *Proceedings of the National Academy of Sciences of the United States of America*. 2017;114(2):206-14.
18. Aoyagi T, Sato Y, Toyama M, Oshima K, Kawakami K, Kaku M. Etoposide and Corticosteroid Combination Therapy Improves Acute Respiratory Distress Syndrome in Mice. *J Shock*. 2019;52(1):83-91.
19. de Jong MD, Simmons CP, Thanh TT, Hien VM, Smith GJ, Chau TN, et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nature medicine*. 2006;12(10):1203-7.
20. Hsueh PR, Chen PJ, Hsiao CH, Yeh SH, Cheng WC, Wang JL, et al. Patient data, early SARS epidemic, Taiwan. *Emerging infectious diseases*. 2004;10(3):489-93.
21. Herold S, Becker C, Ridge KM, Budinger GR. Influenza virus-induced lung injury: pathogenesis and implications for treatment. *The European respiratory journal*. 2015;45(5):1463-78.

22. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. *New England journal of medicine*. 2020;382(18):1708-20.
23. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *Jama*. 2020;323(11):1061-9.
24. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronaries pneumonia in Wham, China: a descriptive study. *The Lancet*. 2020;395(10223):507-13.
25. IMAI District Clinician Manual. Hospital care for adolescents and adults. Geneva: World Health Organization. 2020.
26. The fifth version of the COVID-19 flowchart, diagnosis and treatment at the outpatient and inpatient service levels 2020 [Available from: <https://arakmu.ac.ir/vct/fa/news/8414/%D9%86%D8%B3%D8%AE%D9%87-%D9%BE%D9%86%D8%AC%D9%85-%D9%81%D9%84%D9%88%DA%86%D8%A7%D8%B1%D8%AA-%D8%AA%D8%B4%D8%AE%DB%8C%D8%B5-%D9%88-%D8%AF%D8%B1%D9%85%D8%A7%D9%86-covid-%DB%B1%DB%B9-%D8%AF%D8%B1-%D8%B3%D8%B7%D9%88%D8%AD-%D8%A7%D8%B1%D8%A7%D8%A6%D9%87-%D8%AE%D8%AF%D9%85%D8%A7%D8%AA-%D8%B3%D8%B1%D9%BE%D8%A7%DB%8C%DB%8C-%D9%88-%D8%A8%D8%B3%D8%AA%D8%B1%DB%8C>].
27. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Seminars in immunopathology*. 2017;39(5):529-39.

Figures

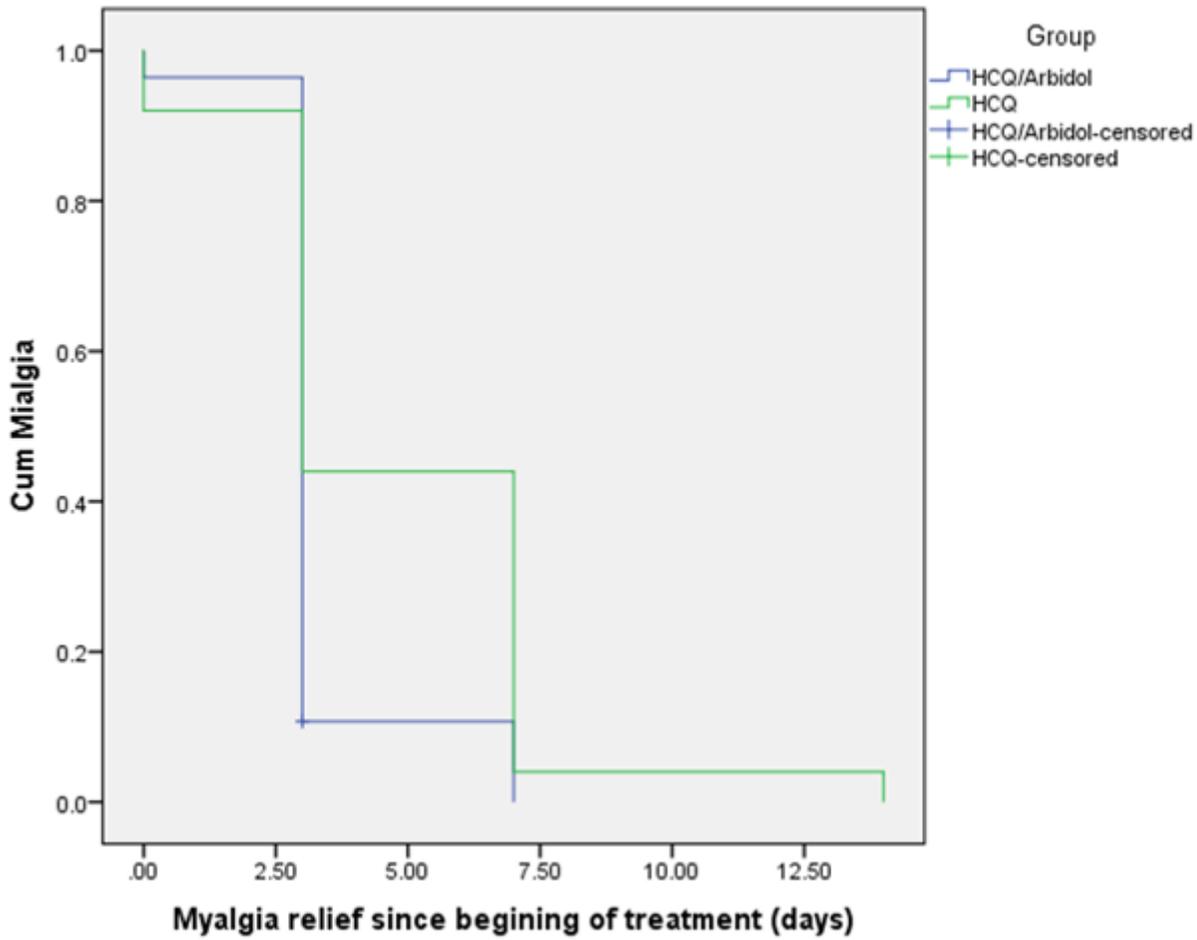


Figure 1

Kaplan-Meier analysis of recuperation Mialgiabetween two groups(who threated with Umifenovir and HCQ and who threated only HCQ).

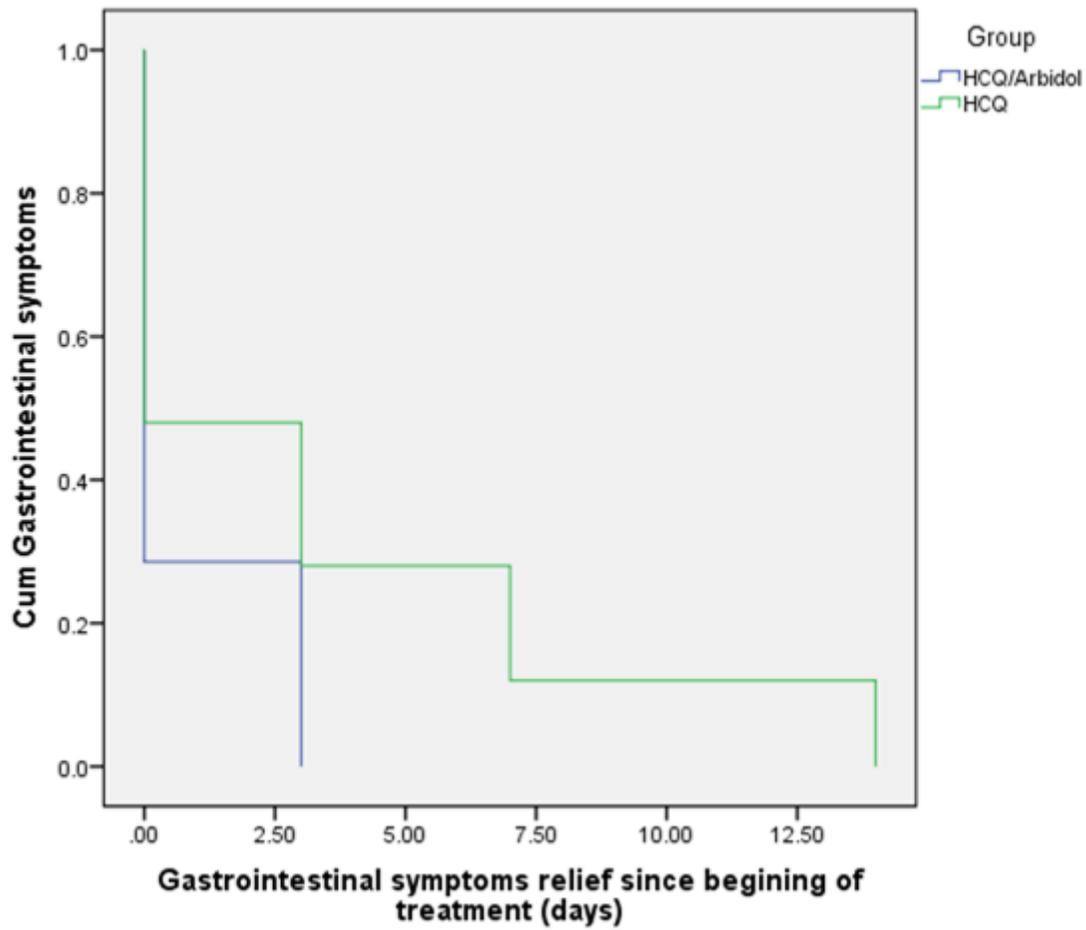


Figure 2

Kaplan-Meier analysis of recuperation GI Symptoms between two groups (who treated with Umifenovir and HCQ and who treated only HCQ).

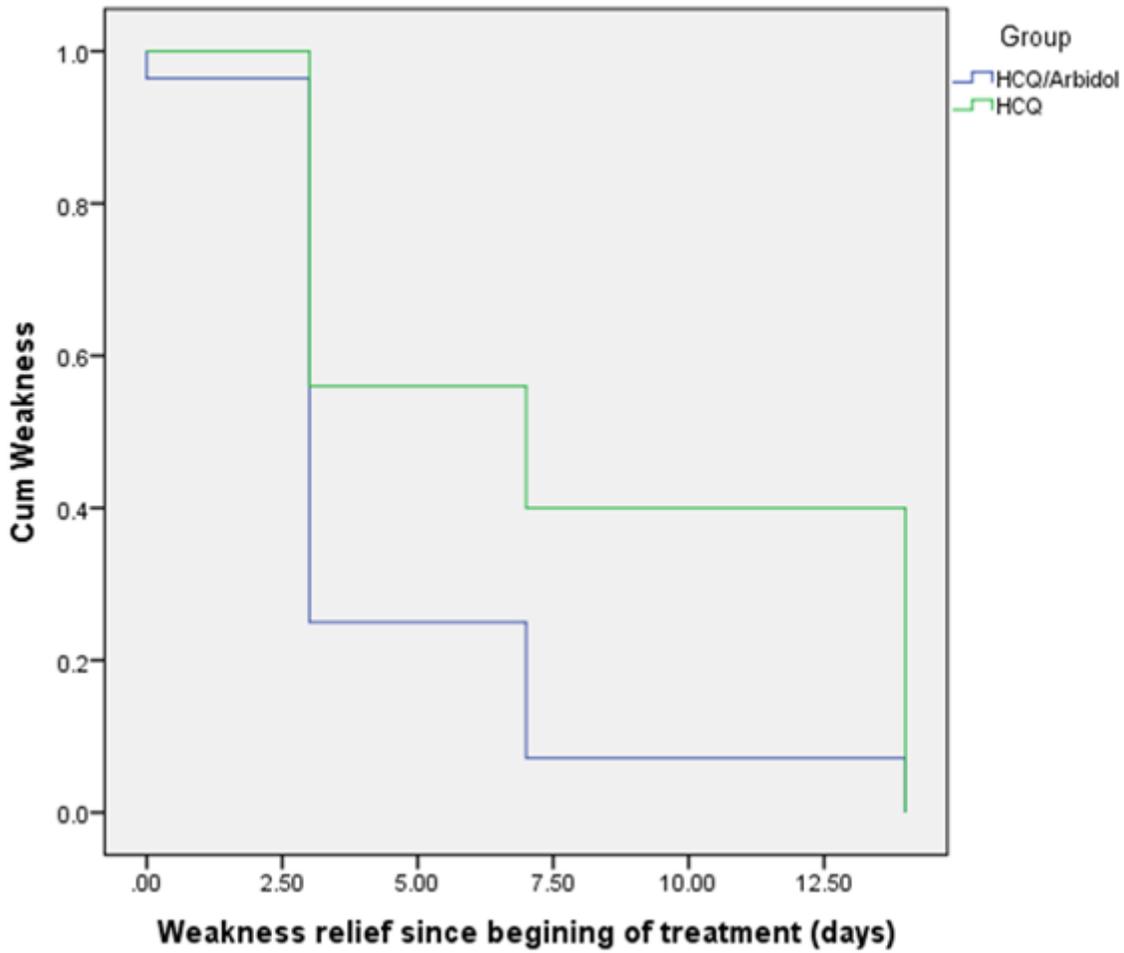


Figure 3

Kaplan-Meier analysis of recuperation Weakness between two groups (who treated with Umifenovir and HCQ and who treated only HCQ).