

Evaluation of the Effect of Prescribed Drugs in the Treatment of Patients with Coronavirus 2019 (COVID-19), At Least 14 Days Follow-Up

Hamed Taheri¹, Ahmad Miri², Amir H Mohagheghi Fard³, Rouhi Afkari^{*4}

¹ Assistant professor of internal medicine, Cellular and Molecular Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.

² Zahedan University of Medical Sciences, Zahedan, Iran.

³ Assistant professor in clinical virology medical school, Zahedan University of Medical Sciences, Zahedan, Iran.

⁴ Infectious Diseases And Tropical Medicine Research Center, Resistant Tuberculosis Institute, Zahedan University Of Medical Sciences, Zahedan, Iran

*** Rouhi Afkari (Corresponding author)**

Infectious Diseases And Tropical Medicine Research Center, Resistant Tuberculosis Institute, Zahedan University Of Medical Sciences, Zahedan, Iran. **E-mail address :**
R.afkari77@gmail.com

ABSTRACT

Background: Coronavirus Respiratory Syndrome is as a cause of severe respiratory infections in human, it is a global threat that can cause respiratory infections such as the common cold, severe acute respiratory syndrome and Middle East respiratory syndrome. The aim of this study was to evaluate the effect of prescribed drugs on the treatment of patients with coronavirus disease 2019 (COVID-19), at least 14 days of follow-up who their infection was confirmed to be positive. In this study, a checklist contains information like demographic, Duration of hospitalization, Cough, Fever, Olfactory-taste disorders, chest X-ray, records were collected from patients and, were analyzed using descriptive statistical methods. The study was performed on 100 Covid-19 patients, with a mean age of 53.49 years. Patients had the initial diagnostic symptoms of Cough, Fever, 84% of whom showed sore throat, and 85% had body pain. 71% of hospitalized patients developed symptoms of Olfactory-taste disorders. Also, the mean length of hospitalization was achieved to be 8.26 ± 1.01 , which decreased according to the type of treatment. In patients who took Remdesivir, Favipiravir, Hydroxychloroquine alone, the mean length of hospitalization was 7.12 ± 1.11 , in patients who took the compound drugs Kaletra, hydroxychloroquine /azithromycin, the average time for hospitalization was declined to 4.22 ± 0.02 while the plasma and interferon takers' groups it was 3.00 ± 0.01 and 2.5 ± 0.09 days, respectively. The study shows that there is a significant relationship between the type of drug used and the shorter course of the disease, which needs further study for better results.

Keywords: Covid-19, Duration of hospitalization, Follow-up, Drugs, Treatment.

INTRODUCTION

Recently, a new coronavirus, called the new coronavirus of 2019, triggered the spread of pneumonia from China to the world, which now poses major health threats to global public health (Dong et al., 2020), (Perlman et al., 2020).

Family and structure of the virus: the new coronavirus is a coated, non-segmented, single-stranded and positive-sense RNA virus with a diameter of 80-120 nm and a viral genome size of 17 to 91 kb which is considered to be one of the largest viral RNAs. The family of

coronaviruses is genotypically and serologically divided into four genera: Alpha, Beta, Gamma, and Delta. The new Coronavirus of 2019 is a coronavirus belonging to the beta coronavirus category. Covid-19 is the third known animal coronavirus after SARS (SARS) and Middle East Respiratory Syndrome (MERS), both of which belong to the beta-coronavirus category (Zhang et al.,2020),(Phelan et al.,2020), (Lu et al.,2020).

Epidemiology and clinical symptoms of Covid-19:Early symptoms of COVID-19 are pneumonia, fever, muscle aches, and fatigue. The incubation period of the disease is 1 to 14 days. The disease begins with a simple respiratory symptom that is accompanied by fever and cough within 2-3 days. Reports indicate that the symptoms of the disease are spreading swiftly and affect not only the respiratory system but also the gastrointestinal tract, multiple senses, and kidneys as well(Chan et al.,2020), (WHO.,2020).

The World Health Organization listed the symptoms of the new coronavirus disease in terms of severity, among other symptoms to be included swelling, pimples, paleness of the fingers and toes, and loss of ability to move or speak(WHO .,2020).

The most common symptoms including fever, dry cough, and fatigue, and the less common symptoms are bruising, pain, sore throat, diarrhea, swelling, headache, loss of sense of smell or taste, and then there are severe symptoms such as difficulty in breathing or shortness of breath, pain and/or pressure on the chest and even loss of ability to move or speak (WHO .,2020), (Wong et al.,2020).

Diagnostic methods:Seropositive studies show that the approach to diagnosing this virus is by using molecular PCR tests, but there are limitations in diagnosing the disease in the early days of infection with the virus (Gao et al.,2020), (Kelly et al.,2019).

Therapeutic and pharmacological methods:To this date, no successful antiviral vaccine for the new and novel coronavirus-19 infections has been clinically confirmed; although, studies in this area have begun and are continuing inside and outside of the country(Water et al.,2020), (Bai et al.,2020).So far, different antiviral drugs have been tested in combination or separately on patients, which has had good results in controlling the disease. The most commonly used drugs for corona patients are of hydroxychloroquine, IVIG, Kaletra (lopinavir + ritonavir), ribavirin, sofosbuvir,daclatasvir, atazanavir, Arbidol, oseltamivir, and azithromycin, as well as limited plasma therapy (WHO.,2020), (Backer et al.,2020).But for out-patient patients, drugs such as oseltamivir, hydroxychloroquine, azithromycin, co-amoxiclav naproxen are being used. A group of researchers examined 42 patients with corona disease, 16 of whom were in the control group and the 26 other patients who took 200 mg of hydroxychloroquine, three times a day for 10 continuous days to investigate the effect of drugs on the Covid-19 virus during a study14-16. Of these, 6 took another drug too called azithromycin. The results showed that people who took both drugs recovered completely after 6 days, but only 1.57% of patients receiving hydroxychloroquine alone were treated (Dorigattiet al.,2020),(Li et al.,2020).According to the researchers, 12.5% of the patients in the control group completely recovered from the coronavirus. Therefore, the researchers concluded that the combination of two drugs, hydroxychloroquine, and azithromycin, can greatly help people with Covid-19; On the other hand, many drugs have been tested as anti-corona drugs have had little effect on patients' recovery (Swerdlowet al.,2020), (WHO.,2020).Extensive research on the new coronavirus-19 is needed to fully elucidate its route of transmission and its pathogenic mechanisms, and to identify potential drug targets that can be effective in developing common preventive and therapeutic measures. Li et al. recently reported that two drugs, Remdesivir (GS-5734) and chloroquine (CQ) phosphate effectively inhibit SARS-CoV-2 infection in vitro (Ahmed et al.,2020),(Li et al.,2020).

Remdesivir is a US-made nucleoside analog product. A recent case study showed that Remdesivir's treatment improved the clinical condition of patients infected with SARS-CoV-2, and a third phase clinical trial of Remdesivir against SARS-CoV-2 began on February 4 in Wuhan (Modjarradet al., 2019), (Yong et al., 2019), (Xu et al., 2020).

However, between the two potential drugs, CQ seems to be more preferable for large-scale usage due to its availability, proven safety records, and relatively low cost. Based on preliminary clinical data, CQ has been added to the list of experimental drugs in the Sixth edition guidelines for the diagnosis and treatment of COVID-19 published by the National Health Commission of the People's Republic of China. Several drugs such as chloroquine, Arbidol, Remdesivir, and Favipiravir are currently undergoing clinical trials to test their efficacy and safety in the treatment of coronavirus 2019 (COVID-19) (Tang et al., 2020), (Liu et al., 2020). So far, promising results have been achieved. This study aims to evaluate the history and effect of prescribed drugs on the treatment of 100 COVID patients with at least 14 days of follow-up.

METHODES

1-2. Study design and participants: The study was conducted at the University Hospital Institute BouAli in Zahedan, Iran. Patients with PCR-documented SARS-CoV-2 RNA from a nasopharyngeal sample were admitted to our infectious diseases (ID) ward.

2.2. Clinical classification and clinical follow-up: The design for the present descriptive study was cross-sectional with a 14-day follow-up on patients with corona disease who referred to the hospitals of Zahedan University of Medical Sciences as probable or suspected cases of corona and after performing a molecular test, their infection was confirmed to be positive. They were hospitalized, and after recovery and discharge from the hospital, they have accommodated in a makeshift the convalescent home for a certain period, according to the doctors' discretion. According to the CDC-2020 and WHO's guidelines, "a definite patient with Covid-19 is a person who has received laboratory confirmation of the presence of the Corona infectious virus, regardless of the clinical symptoms. This study is composed of two phases. In the first phase: all participants included in this study diagnosed with corona positive and were hospitalized until recovery. In the second phase, after recovery and discharge, the patients were quarantined at home or hospital convalescence for 14-24 days. In this study, a checklist contains information like Sex, Age (years), Duration of hospitalization (days), Chronic Dialysis Patient, Hx of Ischemic Heart Disease, Hx of Diabetes mellitus, Hx of COPD, COPD duration (months), Cough, Fever, Nausea/ vomiting, diarrhea, body pain, Anosmia, maximum CRP, Olfactory-taste disorders, Rheumatologic Disease, Malignancy, Dyspnea, Sore throat, Chills, chest X-ray, vitamin D level (ng / L) (the first day of admission), vitamin D level (ng / L) (after hospitalization), Asthma, Taking any asthma medication, Tuberculosis, Taking any TB drug as well as the history of smoking, drug use and alcohol consumption records were collected from patients' files and upon entering the data in the SPSS software version 17, they were analyzed using descriptive statistical methods.

3-2. Chest Computed Tomography: Patients systematically underwent an unenhanced chest low-dose computed tomography (LDCT) upon admission or soon after, using a single CT machine. All images were analysed by experienced chest radiologists, then classified as compatible or not compatible with pneumonia (WHO., 2020), (Li et al., 2020).

4-2. PCR assay: Nasopharyngeal swabs were collected on a daily basis until discharge with some exceptions. Some discharged patients were also sampled during follow-up at our out-patients department when possible. SARS-CoV-2 RNA was assessed by real-time reverse

transcription- PCR using a hydrolysis probe-based system that targets the gene encoding the envelope (E) protein , as previously described (WHO .,2020), (Li et al.,2020).

5-2. Indication for the hospitalization: The main indication to be hospitalized in the Covid-19 ward was the shortness of breath or an oxygen saturation level less than 93% in room air or (RR> 30 with or without fever). In addition to that, the physician could have admitted the patient based on the patient's clinical condition and paraclinical findings (WHO .,2020), (Li et al.,2020).

6-2. Admission procedure (Patient Flow):Patients who were referred to the emergency ward in the selected hospitals affiliated to Zahedan University of Medical Sciences from outpatient centers had indications or suspected symptoms of Covid-19. They were closely monitored in isolation before the decision to determine for their hospitalization after the paraclinical assessments and x-rays. Meanwhile, they received the necessary supports. If confirmed, definite diagnosis (positive molecular test result) or clinical confirmation (traces of Covid-19 on CT scan) and in cases where there was no molecular test result available but there was a strong suspicion of Covid-19 based on the diagnosis by the physician- here CRP-positive lymphopenia was helpful- afterward, they were referred to Covid-19 ward. In cases of refractory hypoxemia, decreased level of consciousness, hemodynamic instability, hypercapnia - respiratory fatigue, by the diagnosis and discretion of the anesthesiologist, the patient was referred to the intensive care unit. According to the pdf flowchart of diagnosis and treatment of the disease for the outpatient and inpatient services, (July 2020) (WHO .,2020),(Li et al.,2020).

7-2. The crucial treatments at the time of hospitalization: According to the recommendations of the National Scientific Committee, it could be prescribed exclusively for hospitalized patients:

1-Kaletra (lopinavir + ritonavir), hydroxychloroquine and azithromycin, atazanavir/ritonavir, Remdesivir, favipiravir

2. Kaletra tablets (Lopinavir / Ritonavir 50/200) mg every 12 hours 2 pills after a meal for at least 7 days and a maximum 14 days

3- tablets (Atazanavir / Ritonavir 300/100) One tablet daily with food or Atazanavir 400 mg daily at least for 7 and at most 14 days

4-Interferon beta-1b (IFN β -1b) 250 micrograms by subcutaneous injection every other day in 5-7 doses

5-Interferon beta-1a (IFN β -1a) 44 micrograms by subcutaneous injection every other day in 5-7 doses(WHO .,2020), (Li et al.,2020).

8-2. Hospital discharge criteria: After hospitalization of patients with Covid-19 in the hospital and passing the treatment and recovery periods, only with the following terms and with the discretion of the relevant physician, the patient was allowed to be discharged:72 hours after cessation of fever without the help of antipyretic, 93%> 2POS without ventilator in room's air, Improvement of the patient's respiratory/ vital clinical signs at the discretion of the physician, after discharge from the hospital, the recovered patient was transferred to the convalescent ward of the hospital or to quarantine at home with the necessary recommendations(WHO .,2020), (Li et al.,2020).

9-2. Criteria For Discharge Of Hospital: In this study, criteria for discharge of hospital: patients with two successive negative nasopharyngeal samples resulting from PCR assay (CT value $\geq$ 35) were discharged.

10-2. Criteria to discharge from the recovery ward or quarantine: In general, the criteria to end the patient's isolation were as follows: 1- In symptomatic patients (if the symptoms were not severe): 10 days be passed since the onset of symptoms + at least three days without symptoms) Symptoms include fever and respiratory symptoms (generally this period takes about two weeks. 2- In asymptomatic people: up to 10 days after the RT-PCR test for Covid-19 was positive.

11-2. Statistics: After collecting the data, they were analyzed using the SPSS software ver. 17 by descriptive statistical methods.

12-2-Ethics Statement: The protocol was approved by the ethical committee of the Zahedan University of Medical Sciences (N^o: 1399.106).

RESULTS

1- Demographics and history of the disease: In this study, 100 patients with Covid-19 referred to BouAli Hospital affiliated to Zahedan University of Medical Sciences were studied (n = 100), all of whom were positive for the RT-PCR test. 56% were male (mean age 59/25 $\pm$ 2/010). And 44% female (mean age of 47/74 $\pm$ 1/012) participated in this study. Reviewing the medical records of the patients, their medical records are listed in Table 1.

2-Type of initial diagnostic symptoms: As shown in Table 2, in terms of initial diagnostic symptoms, Cough, Fever, and Dyspnea were observed in all hospitalized patients, also 84% of them had Sore throat and Chills symptoms, 39% had Nausea/Vomiting, and 85%, body pain symptoms.

3- Relationship between hospitalization time and type of drug treatment: The average duration of hospitalization was 8.26 $\pm$ 1/01 (Duration of hospitalization (days)), which decreased based on the type of treatment.

4- assessment of vitamin D level during hospitalization: During the assessment of vitamin D level during hospitalization (on the day of admission), the average level in patients (Vit D level (ng/L) (the first day of hospitalization) was 10.16 $\pm$ 1.102 which was Increased with vitamin therapy to 49/16 $\pm$ 2/012 that was in turn very effective in treatment and improvement of symptoms (Table 2 and 3)

5- History of alcohol and drug use and tuberculosis and asthma: Among the patients studied, 52% had a history of smoking (Smoker), 15% had a history of alcohol consumption and 12% had a history of drug use.

6. The relationship between Covid-19 and blood type: Examining the type of blood in a group of people with Covid-19, it was observed that among the 100 patients, the most type of blood belonged to A (45%).

DISCUSSION

The study was performed on 100 Covid-19 patients with a mean age of 53.49 years of old, with a mean age of 59/25 years for men and 47/74 years for women. According to medical history, 31% had a history of dialysis, 28% had a history of diabetes mellitus, 42% had a history of clogged arteries, and 22% had the chronic obstructive pulmonary disease (Hx of COPD) that on average the duration of it was observed to be 3.12 $\pm$ 1.001 months with a mean age of 60. The results illustrated that the mean maximum CRP level of hospitalized patients was 62.74 $\pm$ 1.918, in 94% of CT of the chest, and was of an atypical type. In the

present study, patients had the initial diagnostic symptoms of Cough, Fever, Dyspnea, 84% of whom showed sore throat and chills, 39% had nausea/vomiting and 85% had body pain. 71% of hospitalized patients developed symptoms of Olfactory-taste disorders and Anosmia. Also, 63% of people were admitted with gastrointestinal symptoms of Diarrhea with a mean age of 45 years, of whom 62% were male. Also, 51% had the symptoms of Rheumatologic Disease and no history of cancer was observed in any of the subjects. The mean length of hospitalization was achieved to be 8.26 ± 2.11 , which decreased according to the type of treatment. In patients ($n = 25$) who took Remdesivir, favipiravir, hydroxychloroquine alone, the mean length of hospitalization was 7.12 ± 1.01 , in patients ($n = 30$) who took the compound drugs Kaletra (lopinavir + ritonavir), hydroxychloroquine/azithromycin, the average time for hospitalization was declined to 4.22 ± 0.02 while the plasma ($n = 20$) and interferon ($n = 25$) takers' groups it was 3.00 ± 0.01 and 2.5 ± 0.09 days, respectively. In a way that in the group treated with plasma and interferon after discharging from the hospital and transferring to a convalescent home (or being quarantined at home), no clinical signs of Covid-19 were observed, while in the group receiving the drugs Kaletra (lopinavir + ritonavir), hydroxychloroquine and Azithromycin, atazanavir/ritonavir recurrence of cough and moderate fever was seen for 48 hours. This is while, in the group receiving Remdesivir, favipiravir, hydroxychloroquine alone, after recovery and discharge from the hospital and accommodating in quarantine, cough and fever were observed for 3 days. Also, among the admitted patients, 18 were referred to the ICU for 5 days, of whom 8 needed a ventilator, which after recovery and approval by the doctor, they were sent to the convalescent ward of the hospital or the quarantine with the special conditions. Also, among the studied patients, 52% observed to have a history of smoking, 15% had a history of alcohol consumption and 12% had a history of drug use, with a history of tuberculosis and asthma obtained 13% and 18%, respectively, 42% of whom had a history of taking immunosuppressive drugs and 52% had a history of steroid drugs. Examining the type of blood in people with Covid-19, it was observed that among the 100 patients, the most common blood type was related to A (45%) with an average age of 51 years, while 18% had blood type B and (29%) enjoyed blood type O and only 8% of them had type AB.

The study conducted by Li et al reported the average of 425 patients' age infected with new coronavirus-19 at 59 years, of whom 56% were male, the mean incubation period was 5.2 days, and approximately half of adult patients were 60 years and older. In the early stages, the number of infected patients doubled every 7.4 days. The rate of disease transmission from the infected person was 2.2. Although 55% of the first patients infected with new coronavirus-19 were related to the Hanan seafood market, the number of unrelated cases has increased exponentially (logarithmically) since late December 2019 (Huang et al., 2020). Of the 41 patients with new coronavirus-19 infection in their study, Huang et al. showed that 73% of patients were male and 32% of them had underlying diseases including diabetes (8 patients), hypertension (6 patients), and (6 patients) with cardiovascular diseases. Their average age was 49 years old. Of the 41 patients, 27 were related to the Hanan seafood market. The mortality rate of patients with new coronavirus-19 was reported to be 15% in this study [27-29]. In a follow-up study, Wu and Gautret et al. reported that 80 corona patients who were treated with hydroxychloroquine and azithromycin (for minimum 3 days, and maximum 6 days) from the beginning of the study, with the average age of 52 years showed high hypertension, diabetes, and chronic respiratory disease as high-risk factors for the severe form of Covid-19. The time between the first symptoms of the disease to hospitalization was 5 days on average, and the maximum time was 17 (Wu et al., 2020), (Gautret et al., 2020), (Haghighbayan et al., 2021). 53.8% of patients showed symptoms of LRT1 and 41.2% symptoms of URTI, and only 15% of patients had a fever. 4% were asymptomatic patients with a

positive RT-PCR test result. Also, a high percentage (92%) of low NEWS, 53.8% showed LDCT similar to pneumonia. The average time between the onset of symptoms and the start of treatment was 4.9 days, and 93.7% of patients were treated on the same day or one day after admission. 79 out of 80 patients received daily treatment, with an exception of one patient who was excluded from treatment on day 4 because of drug interactions with rare drug complications. Also, from 65 hospitalized patients, the average time to start treatment until discharge was 4.1 days and a maximum of 4.6. The majority of patients (81.3%) had satisfactory results and were discharged from the hospital with a minimum NEWS score with only 3 patients who were referred to ICU among whom one patient was later referred to the general ward. An 86-year-old patient who was not transferred to the ICU expired in the general ward (Gautret et al., 2020), (Ji et al., 2020). In a descriptive study of 138 patients with COVID-19 pneumonia in Wuhan, the most common clinical features at the onset of the disease were: 99% reported fever, 70% fatigue, 59% dry cough, 40% anorexia, 35% muscle soreness, 31% shortness of breath, and 27% sputum production. Shortness of breath developed in 31% after an average of 5 days of illness and continued. Acute respiratory distress syndrome occurred in 20% and mechanical respiration was performed in 12.3%. Other cohort studies of patients with Covid-19 approved in Wuhan reported a similar range of clinical findings. Fever, however, may not be a general symptom (Chan et al., 2019), (Ji et al., 2020). In one study, fever was reported in almost all patients, but approximately 20% of those with a very mild fever was less than 100.4 degrees Fahrenheit or 38 degrees Celsius (Wang et al., 2020), (Li et al., 2020). In another study on 1,099 patients from Wuhan and other parts of China, fever (as the underarm temperature of more than 99.5 degrees Fahrenheit/ 37.5 degrees Celsius) was present in only 44% of hospitalized but eventually it was present in 89% of patients throughout hospitalization. Other less common symptoms include headache, sore throat, and runny nose. The results of the present study have two considerable points: The first is the type of drugs prescribed at the time of hospitalization, which had a direct effect on faster recovery and makes shorter hospitalization in patients. Chloroquine/azithromycin, atazanavir/ritonavir reduced the length of hospitalization compared to the group taking Remdesivir, favipiravir, hydroxychloroquine alone. The second point is that the duration of accommodation and not-recurring or recurrence of the disease in the isolated ward (hospital convalescent or being quarantined at home) can be directly or indirectly affected by the type of medications applied at the time of hospitalization, duration of medication in time of hospitalization, type of care and protocols used during follow-up and accommodation in isolation, full observance of healthy, nutritional and medical recommendations under the supervision of the physicians, consumption of vitamins C, D at the time of hospitalization as well as during accommodation in isolation. Also, increasing self-confidence and the spirit of overcoming the disease is very effective in the recovery process of patients.

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Table 1: The Demographic characteristics of patients.

	Sex		Age (years)	Duration of hospitalization (days)	Chronic Dialysis Patient?	Hx of Diabetes mellitus?	Hx of Ischemic Heart Disease?	COPD duration (months)	Hx of COPD?
	Male (%)n	Female (%)n	Mean±SD	Mean±SD	(%)n	(%)n	(%)n	Mean±SD	(%)n
	56	44	41.74±1.05	8.26±1.01	31	28	42	3.12±1.01	22
Total	100		100	100	100	100	100	100	100

Table 2 : The Clinical characteristics of the studied patients

Tuberculosis (%)n	13
Taking the drug TB (%)n	13
Asthma (%)n	18
Taking asthma medication (%)n	18
Smoker (%)n	52
Addiction (%)n	12
alcohol consumption (%)n	15

Table 3 : The Vit D level (ng/L) in patients with COVID-19

Vit D level (ng/L) (the first day of hospitalization) Mean±SD	Vit D level (ng/L) (after of hospitalization) Mean±SD	(Blood type)			
		A (%) n	B (%) n	AB (%) n	0 (%) n
10.16 ±0.02	49.16 ±2.01	45	18	8	29

*significant

Table4: The relationship between the kind of drugs and the length of hospitalization

Number (n)%	Kind Of Treatment	The mean length of hospitalization (days)	P _{value}
(25)25	Remdesivir, Favipiravir, Hydroxychloroquine Alone	7.12± 1.11	S*
(30)30	The Compound Drugs Kaletra (Lopinavir + Ritonavir), Hydroxychloroquine / Azithromycin	4.22± 0.02	S
(20)20	The Plasma	3.00± 0.01	S
(25)25	Interferon	2.5 ± 0.09	S