

The Significance of Remdesivir and Favipiravir Therapies to Survival of COVID-19 Patients

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The coronavirus disease 2019 (COVID-19) pandemic and the infection escalation around the globe encourage the implementation of the global protocol for standard care patients aiming to cease the infection spread. Evaluating the potency of these therapy courses has drawn particular attention in health practice. This observational study aimed to assess the efficacy of Remdesivir and Favipiravir drugs compared to the standard care patients in COVID-19 confirmed patients. One hundred twenty-seven patients showed the disease at different stages, and one hundred and fifty patients received only standard care as a control group were included in this study. Patients under the Remdesivir therapy protocol were (62.20%); meanwhile, there (30.71%) were under Favipiravir therapy. From the total number of patients under both protocols, 75.6% of the total patients recovered, and 15.7% were deceased. The mortality rate was shown to be 14 out of 64 patients (22%) in critical COVID-19 patients in the Remdesivir group and 3 out of 37 patients (8%) in the Favipiravir group. Remdesivir drug lowered healing mean time to 6 days in mild-to-moderate. COVID-19 clinical manifestations are different among infected patients, and the therapy required to be carefully designed for critical cases in particular. Remdesivir and Favipiravir therapy tend to have a promising efficacy in reducing the mortality rate and time of recovery, especially among mild-to-moderate patients.

Keywords: COVID-19; Favipiravir; Remdesivir; Survival.

The emergence of a novel pandemic caused by COVID-19 poses a huge burden on humanity's health since the Spanish flu in 1918 exceeding 297 million nearly 7 million casualties by December 2021 worldwide. By first week of February, 2021, confirmed COVID-19 cases reached 106 million, mortality recorded over 2 and half millions worldwide¹. Tremendous global efforts by health workers including clinicians and researchers in an attempt to come up with new drug options to seize the infection spread². Many

clinical trials have been conducted, but the clinical efficacy of any therapeutic agent for coronavirus disease has not been proven yet meanwhile, a few of them (Remdesivir, hINFa-2b, Ribavirin, Chloroquine, and Arbidol) are ongoing investigated under clinical trials for their efficacy against the disease³.

Remdesivir which is an adenosine triphosphate (ATP) structural analog inserted during RNA polymerase instead of the natural substrate into nascent viral RNA resultant in

delayed replication due to termination of the chain leading to viral replication inhibition⁴. Remdesivir was suggested to treat SARS-CoV-2 confirmed infection through viral replication during the first week of the symptoms starts⁵. The purine nucleotide favipiravir ribofuranosyl-5'-triphosphate, often known as favipiravir or T-705, is a prodrug whose active ingredient inhibits RNA polymerase, stopping viral replication^{6,7}. The Japan Pharmaceuticals and Medical Devices Agency approved favipiravir for use in 2014 to treat novel and re-emerging influenza virus infection. In vitro study by Eloy *et al.*, (2020) stated that Favipiravir 50% effective concentration (EC50) against SARS-CoV-2 in Vero E6 cells was 61.88 $\mu\text{M/L}$ ⁸. Favipiravir, which focused on RNA-dependent RNA polymerase (RdRP) to treat influenza A, received approval in Japan with an IC50 range of (0.13 to 0.48 $\mu\text{g/ml}$)⁶. Influenza and SARS-CoV-2 are RNA genomes, they showed similar disease manifestations and organ tropism which they rely on (RdRp) for replication, their inhibitor Arbidol which they license for influenza treatment in Asia like Russia and China as an option of standard care for coronavirus disease^{9,10}. Tocilizumab Actemra[®] by Roche Pharma Company is attached to membrane-bound and soluble receptors of interleukin 6, so it is IgG1 mAb human recombinant. The signaling pathway inhibition leads to the reduction the proinflammator activity of the interleukin 6¹¹.

There are currently significant efforts being made by researchers to carry out clinical trials and research studies to better understand the biology and clinical characteristics of COVID-19¹². Information about the age and gender of patients^{13,14}, as well as the effects of various treatment modalities on morbidity and death^{15,16}. However, to the best of our knowledge, no studies from Iraq have been published to cover these pivotal aspects. Therefore, this observational study presenting the first study from Baghdad province to scrutinize the nature of the COVID-19 infection and to evaluate the impact of the proposed treatment protocols on the treated sample of COVID-19 patients seen in a single center from January to August 2020. The study includes the currently therapeutic regimen used such as Remdesivir, Actemra[®], and Favipiravir and their effect on time of recovery and mortality rate.

PATIENTS AND METHODS

Patients

In this prospective, open-label, single-center observational study, adult COVID-19 patients were included. The total number of the patients randomized in this study were 277 confirmed patients with COVID-19, 127 patients were enrolled under therapy protocols beside the supportive treatment and 150 patients were set as a control group received only standard care (Figure 1). The subjects were residents at Al-Forat General Hospital, Baghdad through January-August 2020. The single center patients were mostly inpatients and few were outpatients. They were classified according to the disease severity into mild-to-moderate patients in which were outpatients and all inpatients were severe and critical patients. The COVID-19 patients were evaluated clinically, radiological and confirmed by laboratory polymerase chain reaction (PCR) testing. According to World Health Organization (WHO) recommendations, the COVID-19 patient's condition was classified as mild, moderate, severe, or critical. The patients were considered recovered according to the symptoms vanishing, radiology of chest x-ray or Computerized tomography scan and PCR clearance. This study was authorized by the scientific committee of the college of science at the University of Baghdad.

COVID-19 Patients Therapy Protocols

If we put in mind that hospital stay was 14 days, and recovery rate from COVID-19 symptoms (fever, fatigue, or coughing) in the treatment groups. Senior medical staff at Al-Forat General Hospital in Baghdad implemented the treatment guidelines in accordance with those that the Iraqi Ministry of Health had approved. The therapies groups were as follows:

Remdesivir therapy (D1 group)

Remdesivir 200 mg (Intra venous injection) as a single dose on daily for 3 days, followed by 100 mg once within 7 days of symptom onset¹⁷.

Actemra[®] therapy (D2 group)

Actemra[®] 80 mg/4 mL (Intra venous infusion bag) as a single dose once. One further Actemra[®] infusion may be given at least eight hours following the initial infusion if clinical signs

or symptoms continue to deteriorate or do not improve after the first dose. *Favipiravir therapy (D3 group)*

The Favipiravir dosage is the same as the recommended amount for treating influenza, which is 1600 mg given twice daily on day one and 600 mg given twice daily on day two. Favipiravir treatment lasted between 7 and 14 days.^{18,19}

Control group

According to each patient's clinical status, the patients in this group only received standard care, which may have comprised all of the following or some of them. The standard of care for SARS-CoV-2 often included supportive therapies such oxygen therapy, antibiotic and anti-inflammatory drugs, and symptomatic medicines, as well as some dietary support. According to the disease severity, patients were provided with COVID-19 standard care adopting the 4th edition of The Protocol for Diagnosis and Treatment of Novel Coronavirus Pneumonia (Table 1).

Assessing study endpoints

The mortality rate and the recovery time were assessed in current study. For each of the

three protocol therapies, the patients' survival, progression, and/or recovery were compared to those receiving only conventional treatment in the control group.

Recovery Time

The time required to heal from the time of taking therapy.

Mortality Rate

The patients with mild-to-moderate, severe, or critical patients in therapy protocol group comparing to controls.

Statistical analysis

The PSS software Version (SAS Institute, Cary, North Carolina) was used to perform the statistical analyses, two-sided, with $p < 0.05$ being considered statistically significant. Continuous variables were presented with mean \pm standard deviation, and compared with independent t-test. Count (percentage) was used to summarize the categorical variables comparing with Chi-square tests.

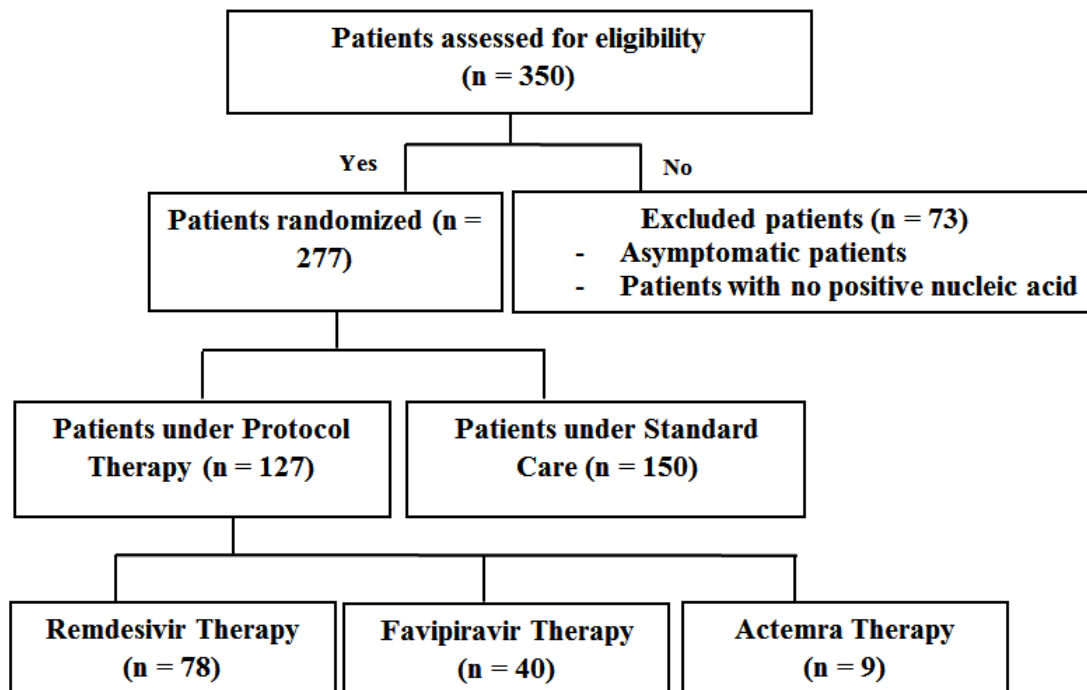


Fig. 1. Study flow chart

RESULTS

Patients’ clinical characteristics

About 127 COVID-19 patients were enrolled; their average age was 46.7 years, and they ranged in age from 23 to 87 years. Of these patients, 37% were men and 63% were women. The controls age and gender were matched, their mean age (50.3.2±9.5 year) with 48% male and 52% females (P> 0.05) (Figure 2) (Table 2). The status of COVID-19 patients through January to August 2020. The percentage of patients under the therapies protocol were shown in Figure 3. There were had high recovery rate with 75.6% and 15.7% of patients were deceased (Figure 4).

Recovery Time

The recovery time was significantly reduced in the Remdesivir therapy (D1) comparing to controls, the mean time in group D1 was 6.23±2.1days, and the recovery mean time in

control group, 3.22±2.1days (P<0.05). Hence, Remdesivir drug lowered healing mean time to 6 days in mild-to-moderate (Table 3).

Mortality rate

The mortality rate was 14/64 patients (22%) in critical COVID-19 patients in D1 group, 3 out of 37 patients (8%) in D2 group, and 3 out of 9 patients (33%) in group D3 (P=0.052). The infected patients taken Remdesivir drug were reduced regarding the death rate especially in COVID-19 critical cases, which in Iraq at the time of performing this observational study was might reach higher than above 50% according to on world data.

DISCUSSION

SARS-CoV2 is novel virus which is require emergence of effective treatment methods, the vaccine was not an option during the first wave

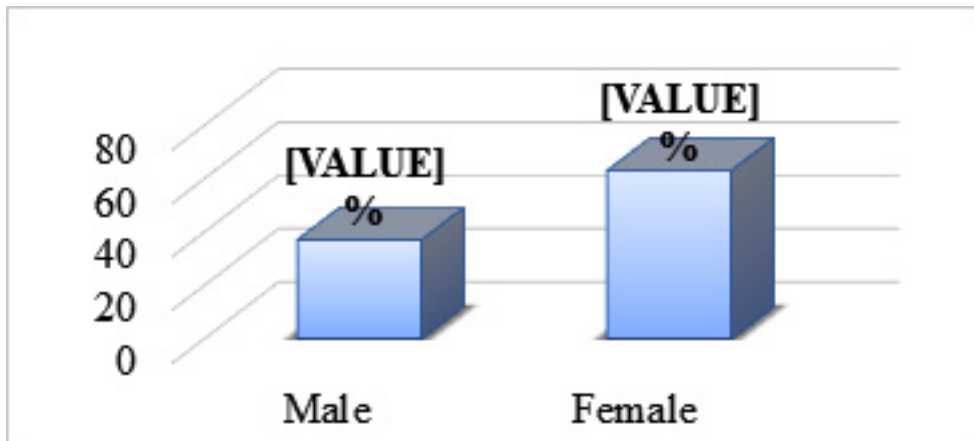


Fig. 2. Gender of COVID-19 patients

Table 1. COVID-19 Patients’ standard care

Medication	Dosage	Recommendations
Acetaminophen	500 mg	On need
Vitamin C	1000 mg	Twice / day
Zinc	75-125 mg	Daily
Vitamin D3	5000 IU	Daily
Azithromycin	250 mg/day	Daily for five days course
Dexamethasone	6 mg	Daily, if needed
Methylprednisolone	40 mg	twice per day, if needed
Oxygen therapy/ C-Pap		If needed
Mechanical ventilation		If needed

of the epidemic. There was an urgently need to a new antiviral agent against SARS-CoV-2 to be applied. In this observational study, the aim was to screen the antiviral therapy protocol since January to end of August 2020 in a single health center (Tables 1 and 2). The COVID-19 treatment current recommendations as in Table 3.

Remdesivir has a high potential in many clinical trials to treat moderate to severe case, lowering required time to improve, and reducing mortality²⁰. A placebo-controlled experiment was done by Beigel *et al.* (2020) on 1062 individuals, 541 of whom were given Remdesivir and 521 received a placebo. The median recovery duration was 10 days (95% confidence interval [CI], 9 to

11 days) for Remdesivir recipients compared to 15 days (95% CI, 13 to 18) for placebo recipients. By day 15, the mortality rate was 6.7% in the Remdesivir group and 11.9% in the placebo group. The study found that Remdesivir reduced the amount of time adults hospitalized with COVID-19 needed to recover more quickly than a placebo²¹.

Spinner *et al.* (2020) conducted a randomized, open-label trial of hospitalized patients in which Remdesivir-treated patients were compared with standard care included 596 patients (including 584 patients with moderate COVID-19), and the trial results showed that patients randomized to a 5-day course of Remdesivir had a statistically significant difference in clinical

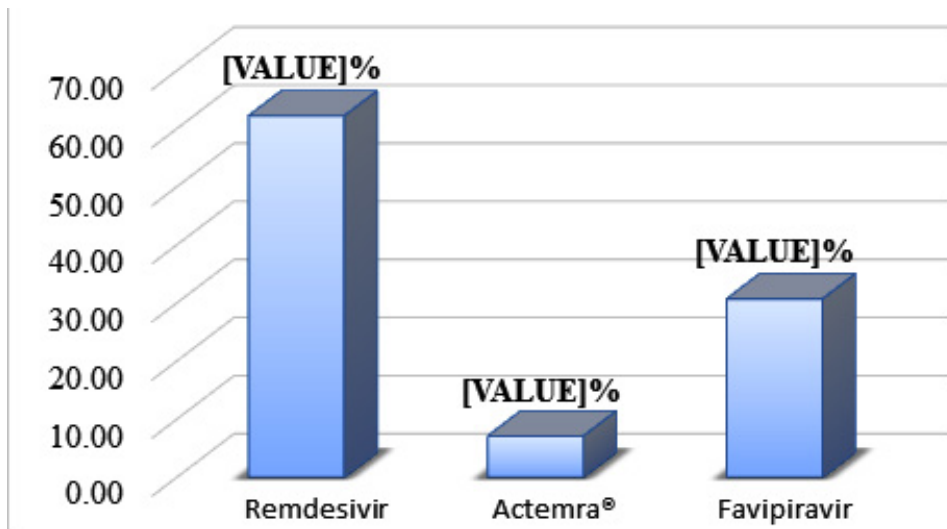


Fig. 3. Patients under the therapy protocols

Table 2. Basic characteristics of the patients

Variables	Remdesivir group (N = 78)	Actemra® group (N = 9)	Favipiravir group (N = 40)	Control group (N = 150)
Gender, n (%)				
Male	34 (44%)	2 (22%)	11 (27%)	88 (59%)
Female	44 (56%)	7 (78%)	29 (73%)	62 (41%)
Age (years), n (%)				
< 65	54 (69%)	5 (56%)	30 (75%)	98 (65%)
≥ 65	24 (31%)	4 (44%)	10 (25%)	52 (35%)
Clinical Classification, n (%)				
Mild-to-Moderate	47 (60%)	6 (67%)	33 (82%)	150 (100%)
Sever	17 (22%)	0	4 (10%)	0
Critical	14 (18%)	3 (33%)	3 (8%)	0

status compared with those receiving standard care.²² The aforementioned clinical trials come in close contact with what this observational study try to highlighted in this single center (Al-Forat General Hospital) which is worked in line with international protocols (COVID-19 Treatment Guidelines Panel, 2021)²³.

It is important to note that this study concurs with a local study carried out by Darweesh *et al.* (2021) in the Kirkuk province, which highlighted the effectiveness of five different therapeutic protocols adopted by the healthcare system in Iraq in reference to WHO guidelines for management of COVID-19 infection and its

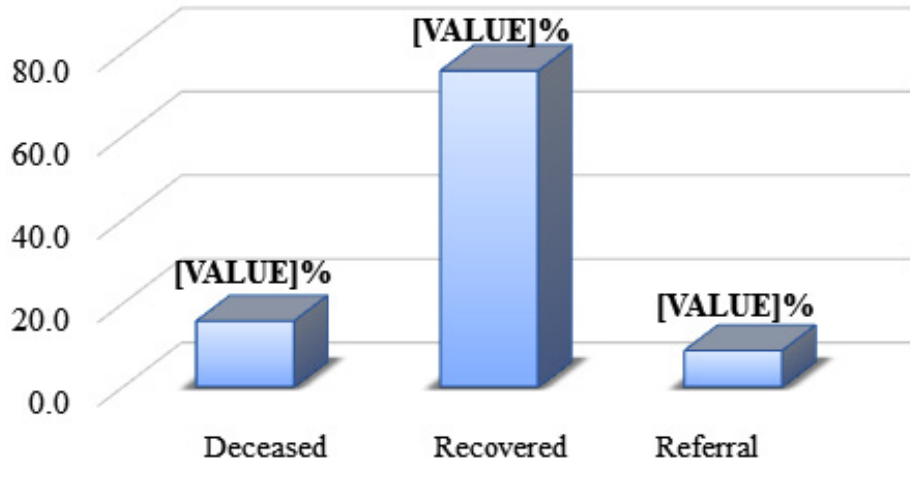


Fig. 4. COVID-19 patients' status under the protocol therapy

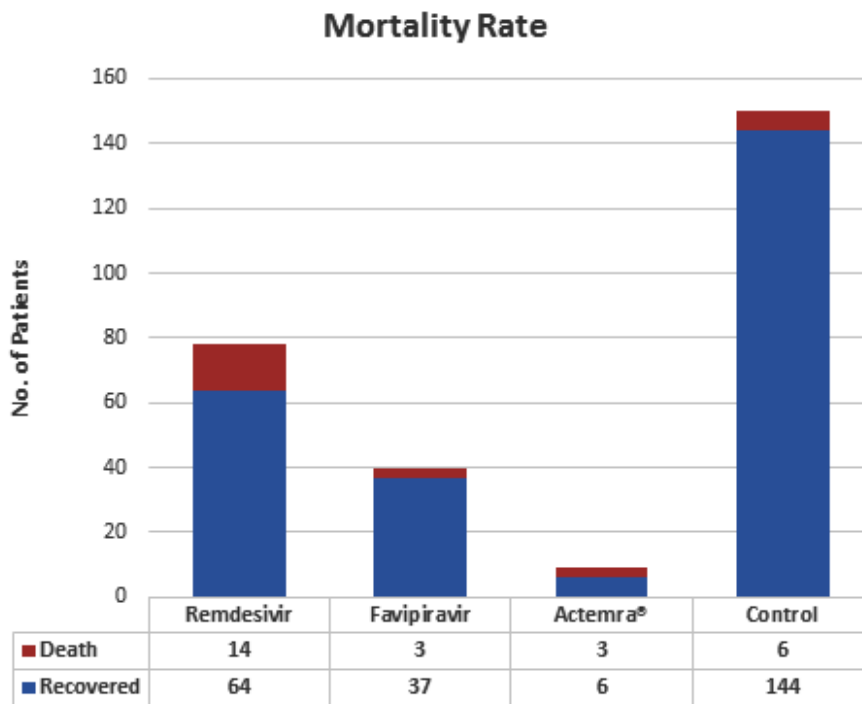


Fig. 5. Mortality rate of patients with COVID-19 under the protocol therapy and control group

Table 3. Time of recovery of COVID-19 patients (Days) in protocol therapy

Variables	Patients subgroup	Remdesivir	Actemra®	Favipiravir	Control
Total	N = 127	N = 78	N = 9	N = 40	N=150
Time of recovery (day)	Total	8.52±5.2	5.33±2.2	16.9±5.4	3.22±2.1
	Mild-to-Moderate	6.23±2.1	0	12.44±6.6	5.24±3.2
	Sever	17.25±8.2	3.24±3.4	21.20±8.7	0
	Critical	15.75±3.4	0	0	0

relationship to mortality rate. This information may be useful for doctors and healthcare providers in choosing the most appropriate therapeutic regimens²⁴.

However, this study disagrees with Goldman *et al.* (2020) study, which performed an open-label trial among 397 patients underwent randomization compared to standard care to evaluate the efficacy and safety of treatment with Remdesivir for 5 or 10 days in patients with severe COVID-19 patients. This study came to the conclusion that severe COVID-19 patients did not need the mechanical ventilation and that there were no significant differences for the both course duration of Remdesivir²⁵.

A study by Chen and colleagues (2021), in China carried out open-label trail in multi-center to evaluate 2 therapy protocols for treating COVID-19 confirmed patients (Favipiravir Versus Arbidol), included 240 patients. Those under Favipiravir revealed tendency toward improvement in a week period, especially moderate case (71%) versus (56. %) respectively, as well as an earlier lowered in temperature and cough clearance²⁶. Another open-labeled nonrandomized study by (Cai *et al.*, 2020) from China compared the effect of Favipiravir Versus lopinavir/ritonavir among mild-to-moderate COVID-19 cases. The study included 56 patients in which 35 patients were treated by Favipiravir. The authors concluded to safety of Favipiravir administration with no side effects. Favipiravir was used to treat 68% of patients' fevers, which resolved in 3 days as opposed to 6 days in the control group (standard of care).²⁷.

The systematic and meta-analysis review conducted by Manabe *et al.* in 2021 concluded that Favipiravir had a great promise for treating COVID-19 patients. Favipiravir enhanced viral clearance in patients with mild-to-moderate COVID-19 after 7 days of treatment, which is

consistent with the results of this observational trial^{28,29}. According to Brahmantya *et al.* (2021), oseltamivir or favipiravir, which is regarded as administering an antibiotic and has become routine therapy in Indonesia, is the antiviral that is advised in that country. Oseltamivir or favipiravir are still prescribed according to the Indonesian COVID-19 management guideline, despite the fact that the WHO does not advise doing so³⁰.

A meta-analysis of observational studies investigating the effectiveness of tocilizumab on COVID-19 patient mortality was carried out by Malgie *et al.* in 2021. Ten studies including Tocilizumab therapy were included in the analysis, totaling 1358 patients. The findings showed that Tocilizumab group mortality was lower than control group mortality. Patients who took tocilizumab had a mortality rate that was (12%) lower than that of controls³¹. Ten randomized controlled trials examining Tocilizumab's effectiveness in COVID-19 patients were included in a review by Arthur *et al.* (2021). Standard care was provide to the control group. The primary findings were recorded mortality in the (28 to 30 day). A nearly 6500 were enrolled, around 3400 patients (52%) were treated by Tocilizumab. The therapy group was declined mortality (24 % *versus* 29%)³², meanwhile; Rosas *et al* (2021) study findings was not conclusive, mortality at day 28 was (20 %) under the Tocilizumab therapy and (19%) under the placebo³³. Due to the few numbers of patients included in the current observational study who had been given Tocilizumab, we can roll out the efficacy effect of Tocilizumab.

Study limitations

This study has a number of limitations, including the observational design, which may not account for all risk factors other than age, gender, and clinical classification, such as co-existing chronic conditions, which frequently necessitate

the referral of patients to hospitals with a higher level of expertise. Second, it is exceedingly challenging to undertake a thorough study in the midst of such a public health catastrophe. Third, given the length of the patient's hospital stay, the follow-up period was quite brief. Four, access to such information is closely controlled by higher authorities and was at times prohibited in the initial few months of the pandemic. The data were gathered based on hospital registry data.

CONCLUSIONS

Health care providers are facing tremendous efforts in supplying pharmaceutical care. The symptomatology of COVID-19 are varied among patients, the therapy required to be designed towards certain symptoms as well as towards the progression of the infection among patients. Remdesivir and Favipiravir therapy tend to have a promising efficacy in reducing the mortality rate and time of recovery especially among mild-to-moderate patients.

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Conflict of Interests

The authors claim that there are no conflicting interests.

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