**Changes in Pharmacological Approach to COVID-19 in A Referral Hospital in Tehran during Two years**

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**Abbreviations:**

**FDA:** Food and Drug Administration

**WHO:** World Health Organization

**ARDS:** Acute Respiratory Distress Syndrome

**MERS:** Middle East Respiratory Syndrome

**SARS:** Severe Acute Respiratory Syndrome

**PCR**: Polymerase Chain Reaction

**ESR:** Erythrocytes Sedimentation Ratio

**CRP:** C Reactive Protein

**PACS:** Picture Archiving and Communication

**CT-scan:** Computed Tomography Scan

**MRI:** Magnetic Resonance Imaging

**GGO:** Ground-Glass Opacity

**PET:** [Positron Emission Tomography](https://www.cancer.net/navigating-cancer-care/diagnosing-cancer/tests-and-procedures/positron-emission-tomography-and-computed-tomography-pet-ct-scans)

**RNA:** Ribonucleic Acid

**Abstract**

**Aim:** The current study attempts to look at the trend of medication prescription among inpatients with COVID-19 by comparing two groups of them who admitted in our hospital at separate times with around two years interval.

**Materials and Methods:** Through a retrospective cross-sectional design, the current study enrolled hospitalized cases from two separate time sections including winter 2019 and summer 2021 to compare some characteristics of COVID-19 in addition to sex and age distribution as well as the approach and management and their changes as the time passed.

**Results:** Remdesivir was raised to be the most common used medication for COVID-19 after one and a half year when approved by the FDA in this regard. Tocilizumab was prescribed for just less than 6% at earlier pandemic in winter 2019 while used in more than a half of hospitalizations in 2021. After two years, corticosteroids are used in 98.6% of the cases at least in our center.

**Conclusion:** Exact medication administration to target COVID-19 and accurate vaccination in addition to “Herd immunity” among the global population seem to be the chief secret of the current success at least for partial control of the disease now.

**Keywords: COVID-19, Remdesivir, Tocilizumab, Corticosteroids, Medications, Management**

**Background and Objectives**

COVID-19, involving at least 213 countries and territories, emerged in January 2019 to cause totally 423 million worldwide cases and more than 6 million global deaths up to now. Iran has experienced just less than 7 million COVID-19 cases resulting in 135 thousands death as the data shows (1,2). There was a very wide range of different medications prescribed for hospitalized COVID-19 patients regarding the global and national protocols which changed based on new findings and researches as time went on. A vast number of anti-viral and anti-bacterial agents came into use which were known active through previous epidemics and pandemics such as H1N1, SARS-CoV and MERS, etc. Medications like oseltamivir (Tamiflu®) and hydroxychloroquine sulfate and later adding lopinavir/ritonavir (also known as “kaletra®”) were raised much more than other medications regarding their effects on severe influenza for the former and malaria control during previous viral pandemics for the second one (3). Nowadays, after about two years of starting the COVID-19 pandemic, the treatment protocols are totally changed switching the medications from the named ones to drugs like tocilizumab and remdesiver targeting cytokine storm and viral load as well as many other conditions which push the disease to much severe types.

The current study attempts to look at the trend of medication prescription among inpatients with COVOD-19 by comparing two groups of them who admitted in our hospital at separate times with around two years interval.

**Materials and Methods**

Through a retrospective cross-sectional design, the current study enrolled hospitalized cases from two separate time sections including winter 2019 and summer 2021 to compare some characteristics of COVID-19 in addition to sex and age distribution as well as the approach and management and their changes as the time passed.

This study benefited from a registry we established for COVID-19 in our referral hospital using three informative sources which in turn, record clinical, laboratory and radiographic findings for hospitalized patients.

**Subjects:** Totally, our center has welcome more than 6000 COVID cases since winter 2019 which needed too much time to be recorded and studied. The current study enrolled 664 cases including 517 from 2019 and 147 from 2021. All the patients were studied for clinical, laboratory, and radiographic presentations. The study protocol was approved by the local ethics committee at the coordinating center (Shahid Beheshti University of Medical Science) (IR.SBMU.NRITLD.REC.1401.036) and has been performed in accordance with the ethical standards laid down in the 2000 Declaration of Helsinki.

**Clinical information:** All the patients had referral codes to be found in a huge information pool in our tertiary referral university hospital by which we found scanned records to export necessary information including demographics, disease manifestations, general condition, comorbidities, impression and diagnosis, ordered medications, nursing reports, vital sign charts and more. The outcome of hospitalization such as death, ICU admission, and discharge in good condition were found in this field of sources as well.

**Laboratory findings:** There is a bank for laboratory records of the patients using which we gathered many items from blood group and biochemistry, serum concentrations of inflammatory factors like interleukins, D-dimer, ESR, CRP and others beside real-time PCR results for COVID-19 in addition to blood cell count.

**Radiographic findings:** Using a source named PACS, our referral center records all the radiography stereotypes and reports belonging to any radiographic study which were done including plain radiography, CT-scan, MRI, and even PET-scan. Referring to them, we were able to find any CT-scan pattern or finding regarding our variable checklist such as ground-glass opacity (GGO), cavitary lesions, lobar or pleural involvement, and many other signs.

**Results**

We studied 517 records of winter 2019 and compared them with 147 records from summer 2021. Of the total patients, 427(64.3%) were males which doubled the female rate. The most found age category was the group of 60 and older patients with evenly reduced rates to younger patients. The two studied time sections had similar age and sex distributions as can be seen in table 1. The average hospital stay was 8.53±5.57 days and hypertension was the most comorbidity found followed by diabetes mellitus and cardiovascular diseases. Cough and dyspnea were the most symptoms followed by fever, myalgia, chills, fatigue and anorexia which had the same trends in two separate studied time sections.

The most prominent issue was the administered medications to treat the disease when compared between the two time sections evaluated by the current study. Kaletra® (Lopinavir/ritonavir) was the most ordered medication in 2019 in our center along with ceftriaxone and azithromycin followed by hydroxychloroquine and Tamiflu® (oseltamivir phosphate) as found by table 2.

Actemra® (Tocilizumab) was prescribed for just less than 6% at early pandemic in winter 2019 while used in more than a half of hospitalizations in 2021. Favipiravir, rivaroxaban, remdesivir and ribavirin were the other antivirals among which remdesivir was raised to be the most common used medication for COVID-19 after one and a half year when approved by the FDA in this regard.

Another challengeable medication group was corticosteroids which seemed risky early in the pandemic to be picked up only in very sever conditions to save patients’ lives; but now, after two years, is used in just less than 100% of COVID cases (98.6%) at least in our center. Hospital stay, ICU admission, sex contribution, manifestations rates and comorbidities were statistically the same during the two separate time sections we studied.

**Discussion**

The current study tried to compare the approach to COVID-19 and its changes in a 2-year period of time in order to show the challenges in facing a new pandemic in a referral center in Tehran. Despite the statistical same pattern of the disease in two years, our study presented the effect of knowledge and experience and their importance through the management of the pandemic which made a worldwide confusion for a while. As explained before, sex and age distribution were the same among our samples from the two separate studied time sections which was not far from the expectations that the disease would be more common and presented more severity in older individuals due to weak immunity and body resistance finally resulting in more hospitalization and unfortunately death rates, especially among complicated cases.

## There was a long list of risk factors at first either proved by the WHO or introduced by some experts among which ABO blood group was the simplest one. The risk factors are under study yet and nobody could absolutely accept or deny them and the issue is a great controversy due to the confusion the disease has made over the world (4-6). However, our study shows no finding in this matter. On the other hand, pulmonary comorbidities were not serious risk factor of infection which was perhaps the result of more strict care about personal hygiene in that group of people (7,8).

Focusing on the prescribed medications we figured out evolutional changes in approach and management of the disease. Actemra administration, as an IL6 inhibitor, really grew up to 50% after two years compared to 2019 in which was ordered only for just less than 6% of the patients. Many studies and authors have introduced interleukin-6 (IL-6) as the crucial cytokine to push patients to ill and critical situation by driving cytokine storm which is the worst event occurring through COVID-19 to exhaust immune system by occupying vast number of immune factors containing inflammatory and anti-inflammatory ones (9). The named drug, as a monoclonal antibody IL-6 receptor antagonist, is a potential candidate to be approved by the FDA based on its success against cytokine release syndrome which is similar to cytokine storm in COVID-19 (10,11). Antivirals such as favipiravir, tamiflu® (oseltamivir), kaletra® and ribavirin almost vanished from the orders after months when specialists and the world health organization found them inefficient although many studies gave high credits to them at early. Kaletra was one of the most attractive therapies early in the pandemic used pronouncedly in Iran but there was no evidence relating to the beneficial whilst existing some pharmacodynamics concerns about achieving drug concentration in the body to inhibit the virus (12-14). Remdesivir was ordered in just more than 6% in 2019 while it was the most common antiviral prescribed for hospitalized patients in summer 2021 (98.6%) as a choice. This medication was finally approved in December 2020 by the Food and Drug Administration (FDA), as the first choice against COVID-19 as an inhibitor of the viral RNA-dependent, RNA polymerase to interrupt viral replication (15-18). Remdesivir has a background of antiviral activity against SARS and MERS and studies show noted reduction of lung virus levels and lung damage with the drug in non-human primates. Through later studies remdesivir presented 31% faster recoveries and around 5% less death rate with less adverse events comparing with placebo (19).

One of the biggest challenges of COVID-19 approach was to or not to order corticosteroids due to their reciprocal effects. This group of medications may improve wide range of manifestations at the expense of immunity suppression. So, health providers seriously needed to make important and dangerous decision to support or deny them in severe cases. Corticosteroids could save ill patients from death but might accelerate organ damage by handing over the patients to the disease which would be a serious indiscretion. After lots of efforts to assess the risks and advantages of using corticosteroids, this group of medications came out finally brilliant regarding manifestations improvement and keeping ill patients away from ICU admission and finally death to be used in just less than 100% of hospitalized cases (98.6%) (20,21).

Hydroxychloroquine was the other challengeable medication to use in prophylaxis, and in some cases, treatment of COVID-19. In our center, more than 66% of hospitalized patients were ordered by hydroxychloroquine in 2019 before being completely eliminated from the orders in 2021. Hydroxychloroquire was the first recommended medication by the WHO earlier in 2019 not because its potentials for COVID-19 treatment, but based on previous experiences of raised malaria mortality in tropical areas in the world through Ebola pandemic in recent decades. This chiefly led people to use antimalarial drugs although some non-approved effects were seen in COVID-19 prophylaxis and treatment. Although studies reclaim positive effects of it in symptoms improvement, hydroxychloroquire neither reduces the rate of 28-day mortality in COVID-19 nor decreases the need to intubation among the patients while elongates their hospital stay when compared with the standard of care and the results were the same with or without azithromycin (22,23). Azithromysin had no benefit in COVID-19 approach in comparison with the standard care in separate studies as well (24).

Remdesivir has been the only FDA approved choice for COVID-19 up to April 2022. This is while there are strong recommendations against hydroxychloroquine/Chloroquine and/or azithromycine in addition to kaletra (lopinavir/ritonavir) and other HIV protease inhibitors as well as ivermectin and any interferon in COVID-19 treatment or prophylaxis (25-29). However, remdesivir in combination with corticosteroids, especially dexamethasone, although no direct evidence to prove, may benefit in severe cases of the disease or patients who need ICU admission due to severe ARDS (30,31).

**Conclusion:** There was a 2-year challenge to face COVID-19 pandemic not only in diagnosis and prevention, but also in terms of treatment which differed by each finding about the virus characteristics in world sizes to push the states to spend lots of sources in order to finally outgo the virus throughout the war for disease management. Selecting rather right medications against COVID-19 and right vaccination in addition to “Herd immunity” among the global population seem to be the chief secret of the current success at least for partial control of the disease now.

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**Competing Interests**

The authors declare no competing interests.

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**Table 1: Comparison of findings between 2019 and 2021**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **2019 Number (%)** | **2021 Number (%)** | **P Value** |
| **Age****(years)** | **Mean ± SD** | 55.88 ± 15.43 | 56.02 ± 16.04 | 0.921 |
| **15-30** | 26 (5) | 7 (4.8) |
| **31-40** | 66 (12.8) | 22 (15) |
| **41-50** | 92 (17.8) | 30 (20.4) |
| **51-60** | 137 (26.6) | 26 (17.7) |
| **≥60** | 195 (37.8) | 62 (42.2) |
| **Sex** | **Male** | 340 (65.8) | 87 (59.2) | 0.142 |
| **Female** | 177 (34.2) | 60 (40.8) |
| **Outcome** | **ICU admission** | 171 (33.1) | 41 (27.9) | 0.270 |
| **Death** | 79 (15.3) | 14 (9.5) | 0.076 |
| **Smoking** | 39 (7.5) | 11 (7.5) | 0.980 |
| **Opium consumption** | 14 (2.7) | 2 (1.4) | 0.543 |
| **Pulmonary disease** | 57 (11) | 8 (5.4) | 0.044 |
| **Immunocompromised cases** | 1. (2.7)
 | 4 (2.7) | >0.999 |
| **Malignancy** | 17 (3.3) | 4 (2.7) | >0.999 |
| **Diabetes Mellitus** | 144 (27.9) | 42 (28.6) | 0.864 |
| **Hypertension** | 155 (30) | 48 (32.7) | 0.535 |
| **Cardiovascular diseases** | 76 (14.7) | 23 (15.6) | 0.776 |
| **Hepatitis** | 5 (1) | 0 (0) | 0.592 |
| **Fever** | 349 (67.5) | 67 (45.60 | <0.001 |
| **Cough** | 408 (78.9) | 118 (80.3) | 0.721 |
| **Dyspnea** | 407 (78.7) | 118 (80.3) | 0.684 |
| **Chills** | 176 (34) | 43 (29.3) | 0.276 |
| **Fatigue** | 62 (12) | 28 (19) | 0.027 |
| **Sore throat** | 22 (4.3) | 4 (2.7) | 0.397 |
| **Chest pain** | 29 (5.6) | 16 (10.9) | 0.025 |
| **Vomiting** | 50 (9.7) | 27 (18.4) | 0.004 |
| **Sputum** | 55 (10.6) | 26 (17.7) | 0.021 |
| **Anorexia** | 84 (16.2) | 33 (22.4) | 0.082 |
| **Myalgia** | 215 (41.6) | 66 (44.9) | 0.473 |

**Table 2: The frequency of administered medications in 2019 and 2021**

|  |  |  |  |
| --- | --- | --- | --- |
| **Year** | **2019 Number (%)****N=517** | **2021 Number (%)****N=147** | **P Value** |
| **Tocilizumab** | 30 (5.8) | 74 (50.3) | < 0.001 |
| **Favipiravir** | 59 (11.4) | 6 (4.1) | 0.008 |
| **Rivaroxaban** | 9 (1.7) | 2 (1.4) | >0.999 |
| **Oseltamivir** | 319 (61.7) | 0 (0) | < 0.001 |
| **Kaletra** | 445 (86.1) | 0 (0) | < 0.001 |
| **Vancomycin** | 176 (34) | 15 (10.2) | < 0.001 |
| **HydroxyChloroquine** | 344 (66.5) | 0 (0) | < 0.001 |
| **Meropenem** | 220 (42.6) | 8 (5.4) | < 0.001 |
| **Remdesivir** | 32 (6.2) | 142 (96.6) | < 0.001 |
| **Ribavirin** | 98 (19) | 0 (0) | < 0.001 |
| **Ceftriaxone** | 373 (72.1) | 107 (72.8) | 0.878 |
| **Ofloxacin** | 98 (19) | 12 (8.2) | 0.002 |
| **Corticosteroid** | 205 (39.7) | 145 (98.6) | < 0.001 |
| **Azithromycin** | 381 (73.7) | 41 (27.9) | < 0.001 |
| **Methotrexate** | 5 (1) | 0 (0) | 0.592 |