COVID-19 Screening in Rheumatologic Diseases Cases; Special Look at Chloroquine Derivate Use

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Abstract

Background: Among suggested medications for the treatment of COVID-19, chloroquine derivates and angiotensin-converting-enzyme inhibitors (ACEIs)/angiotensin II type 1 receptor blockers (ARBs) are the two medications with conflicting effects on the development of the disease.

Objectives: The present study aimed to evaluate COVID-19 in patients with rheumatic diseases receiving chloroquine derivate.

Methods: Every patient with proven rheumatologic diseases registered in two referral centers in Tehran and Alborz, Iran was enrolled in the present descriptive cross-sectional study between May and June 2020. At first, the symptoms of COVID-19 were assessed, and if a case had suspicious symptoms, reverse transcription-polymerase chain reaction (RT-PCR) COVID-19 tests were done. Demographic and clinical data are documented for every patient. Then, the patients were grouped once according to their COVID-19 infection status and another time according to their hydroxychloroquine use.

Results: 1159 patients enrolled in the study with a mean age of 49.39 years. Frequency of hypertension was 22.17 %, diabetics (9.49%) and 20 (1.7%) patients were positive for COVID-19 testing. The most common symptoms of the COVID-19 positive cases were cough (5.2%) and fever (4%). There was no significant difference in receiving ACEIs/ARBs or other medications between COVID-19 positive or negative patients. Among the patients receiving hydroxychloroquine, 15 patients (1.7%) had proved COVID-19 versus 5 patients (1.7%) who were not receiving these medications (P>0.999).

Conclusion: The present study demonstrated that receiving ARBs or ACEIs was not different among patients with or without COVID-19. Moreover, receiving chloroquine derivate was not related to the development of COVID-19 in patients with rheumatologic disorders.

Keywords: Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Type 1 Receptor Blockers, Chloroquine, Hydroxychloroquine, COVID-19

1. Background

In late 2019, a novel coronavirus infection was reported from China and spread shortly through the entire world. The World Health Organization (WHO) declared the novel coronavirus diseases (COVID-19) outbreak as a global emergency in mid-March 2020.12 As the number of infected cases began to rise around the globe, every research center dealing with COVID-19 patients started publishing about the characteristics of their infected cases and their management strategies. Almost every study about the COVID-19 demonstrated that close contact with confirmed cases or traveling history to areas with a high rate of confirmed cases are the main risk factors for becoming infected.3

Those who become infected may develop a wide range of symptoms with variable severity ranging from...
mild symptomatic presentations to severe or even a lethal disorder. The most common symptoms of the COVID-19 patients reported being similar to other viral respiratory tract infections, including fever, dry cough, and dyspnea. However, some other specific symptoms, including loss of the sense of taste and smell, added to the common respiratory symptoms making the diagnosis more specific. Some studies demonstrated specific factors as risk factors of developing COVID-19. These main risk factors include male gender, smoking, age over 65 years, and previous history of respiratory disease, malignancies, and cardiovascular diseases are considered factors that worsen the prognosis of COVID-19. Regardless of the clinical presentations and risk factors of COVID-19, the main challenging issue behind the novel coronavirus infection is the treatment strategy.

There are many conflicts in using various medications in COVID-19 cases, and it seems that an effective vaccine may be more helpful than routine medications. During the early stage of the COVID-19 pandemic, some studies suggested that an antimalarial drug might prevent COVID-19 or even treat the patients alone or in combination with other drugs. The chloroquine and hydroxychloroquine are the two antimalarial drugs that have antiviral and immunomodulatory effects. While there are not enough studies with robust clinical methodology available for the effectiveness of these drugs in the treatment of COVID-19, early studies demonstrated that using these drugs in combination with antibiotics including azithromycin might be beneficial in treating COVID-19. Similar to every other pharmaceutical therapy, these drugs also have a specific side effect that is mainly cardiac toxicity. The angiotensin-converting enzyme 2 (ACE2) is a cellular receptor expressed on many cells, including respiratory systems cells. These receptors are used as functional receptors by coronavirus for cellular entrance. Angiotensin-converting–enzyme inhibitors (ACEIs) are considered common antihypertensive drugs used in many diseases, including hypertension, heart failure, and kidney diseases.

2. Objectives
Moreover, recent evidence suggested that even using chloroquine or hydroxychloroquine might be harmful to hospitalized COVID-19 patients. While the COVID-19 is still a global concern and also there are some worries about the second waves of the disease soon, studying the effect of chloroquine and hydroxychloroquine in those patients who are receiving these medications as their daily therapeutic regimens for other chronic diseases may provide valuable information within the shortest time. There is no general agreement between ACEI use and the development or severity of COVID-19. Recent human studies indicated that using ACEIs or ARBs may not increase ACE2 expression. Therefore, using these drugs during COVID-19 would be safe. While these drugs are considered routine medications in patients with rheumatologic disorders. Therefore, current study aimed to evaluate the COVID-19 in patients receiving antimalarial drugs as their therapeutic regimen.

3. Methods
3.1. Study Design
The descriptive present cross-sectional study took place in two referral centers in Tehran and Alborz, Iran. Data collected was performed during a month starting from 2 May 2020.

3.2. Study Subjects
The sampling frame of the current study were patients with documented rheumatologic diseases, including SLE, Rheumatoid arthritis, and other related rheumatic disorders. Patient selection was based on census sapling. As this study aimed to obtain a holistic view of the condition, all patients with the documented diagnosis of rheumatoid diseases were included in the study with no exclusion criteria. Those patients who agreed to participate asked about any flu-like or COVID-19 symptoms, and if everyone had suspicious symptoms, filled an informed consent form and tested for COVID-19 by reverse transcription-polymerase chain reaction (RT-PCR) method.

3.3. Measurements
The COVID-19 sampling was performed from the nasopharynx and oropharynx, and the RT-PCR kit (manufactured by Pishtaz Teb, Tehran) was used. Then, every patient received a questionnaire of demographic and medical data. The medical data consisted of any medical comorbidities, medication history, signs and symptoms of COVID-19, and risk factors of developing the disease, including close contact with family members who had COVID-19, using public transport services, and participation in any indoor meeting. Then, patients were grouped once according to COVID-19 infection status, another time according to their chloroquine or hydroxychloroquine use before acquiring the disease of COVID-19 pandemic. Although these two medications are among the routine medications in patients with rheumatoid arthritis, there are cases where these medications have been stopped due to side effects or contraindications. The differences between study groups were analyzed by SPSS software (version 20), and P value >0.05 was considered statistically significant.

3.4. Statistical Analysis
Descriptive statistics were presented using mean and standard deviation for continuous variables and frequency and percentage for categorical variables. Comparison of the mean values for the continuous variable (age) between groups was performed using the independent student t-test. The relationship between categorical variables and the study outcomes (COVID-19 incidence and history for medication usage) was evaluated using the chi-square or Fisher exact tests. Data analysis was performed using...
the statistical package for social sciences (SPSS) software version 16 (IBM Inc. Chicago, Il, USA). The level of statistical significance was considered as $P<0.05$.

4. Results
The total number of 1159 subjects enrolled in the present study. Most of the patients were female (81.6%). The mean age of the study subjects was 49.39 ± 0.41 years old. The Demographic, medical history, and clinical characteristics of the study subjects are presented in Table 1.

Twenty (1.7%) out of 1159 patients were positive for COVID-19 testing. The most common symptoms of the study population were cough (5.2%) and fever (4%). The most common medication used among the study population was prednisolone (70.29%) and vitamin D supplementation (57.81%).

A total of 868 (74.9%) of the subjects used hydroxychloroquine. The relationship between study variables and drug usage is presented in Table 1. There was no significant relationship between hydroxychloroquine use and the incidence of COVID-19 ($P>0.999$).

The relationship between study variables and the incidence of COVID-19 is presented in Table 2. Table 2 showed that none of the study variables were significantly related to the incidence of COVID-19. Therefore, no further adjustment was made for possible confounders.

5. Discussion
The present study demonstrated that among our study population with rheumatologic disorders, only 1.7% had COVID-19. Moreover, our result showed that there is not any significant relation between receiving hydroxychloroquine and the development of COVID-19.

After the rapid spread of COVID-19 around the world since late 2019, the central management of COVID-19 patients is mainly supportive care. Patients with mild symptoms can be managed by self-isolation and home care, including using analgesics, antipyretics, and adequate hydration. Patients with more severe presentations may require hospital admission and close monitoring of vital signs. These patients are at increased risk of developing respiratory insufficiency and benefit from oxygen support. Alongside the supportive treatment, researchers are searching for a treatment regimen for COVID-19. Antimalarial medication has been among the available treatment regimens among well-known candidate drugs with various beneficial effects in treating diseases since decades ago. Chloroquine or hydroxychloroquine are antimalarial drugs used to treat chronic diseases, especially autoimmune diseases, including lupus and rheumatoid arthritis. These drugs are thought to inhibit virus fusion with host cells and inhibit nucleic acid replication in host cells. During the early days of the outbreak, multicenter clinical trials from China demonstrated the safety of using chloroquine phosphate in managing COVID-19 pneumonia. Earliest reports revealed that more than 100 patients benefited from this drug in managing inhibiting pneumonia exacerbation and shortening of the disease course without any significant side effects.

Since then, some expert consensus in different countries, including China, Italy, and Germany, suggested using Chloroquine derivatives for patients with different grades of severity. The most recent systematic review on the effectiveness of chloroquine or hydroxychloroquine evaluating seven completed clinical trials demonstrated that using these drugs is superior to supportive care or using Ritonavir/Lopinavir in COVID-19 patients. However, the authors stated that these studies had a considerable risk for bias and methodological shortcomings. Therefore, the authors suggested that considering a therapeutic use of these drugs in daily practice should be made with caution until the ongoing trials become complete. Since then, some studies demonstrated the other side of the coin for using chloroquine or hydroxychloroquine in COVID-19 patients. Boulware et al reported that using hydroxychloroquine after moderate to high-risk exposure with COVID-19 patients might not prevent the illness. Using hydroxychloroquine as a post-exposure medication within the first four days of exposure did not prevent disease development. Another study by Mehra et al evaluated the effect of chloroquine or hydroxychloroquine in hospitalized COVID-19 patients. They demonstrated that using these antimalarial drugs with or without macrolide would not be beneficial.

Their study showed that using these drugs might be associated with cardiac toxicity. The concern about using chloroquine derivate became more evident after this large-scale study demonstrating increased mortality and arrhythmias, and soon, WHO halted testing for hydroxychloroquine in COVID-19 patients.

It is noteworthy that according to our results and the studies similar to Mehra et al study, we might conclude that using 4-aminoquinolines may be a double edge sword in COVID-19 patients. It is still unclear that whether the immunomodulatory and antiviral effect of 4-aminoquinolines worsen the severity of COVID-19 in some patients with previous myocardial injuries that thought to be a common problem in COVID-19 patients. Even more, using other drug agents, including azithromycin that has sodium channel blocking effects may worsen the adverse effects of chloroquine or hydroxychloroquine on cardiovascular system.

Similar to using chloroquine-derived in COVID-19 patients, using ACEIs during COVID-19 is a conflicting issue. Our study revealed that using ACEI or ARBs is not related to COVID-19. Mancia et al demonstrated that as cardiovascular diseases are more prevalent in COVID-19 patients, these patients are more commonly using ACEI. However, they reported that there is no link between using these antihypertensive agents and development of COVID-19. Later studies demonstrated that using ACEI may increase the T lymphocyte counts and decrease viral load peak in comparison with other antihypertensive drugs. Meng et al demonstrated that using ACEI or...
### Table 1. Characteristics of Study Population Based on Receiving Chloroquine Derivate

| Item                              | Hydrosxychloroquine (Yes) (n=868) | Hydrosxychloroquine (No) (n=291) | Total (n=1159) | P Value |
|-----------------------------------|-----------------------------------|-----------------------------------|----------------|--------|
| **Demographical Variable**        |                                   |                                   |                |        |
| Gender                            |                                   |                                   |                |        |
| Male                              | 129 (14.9)                        | 84 (28.9)                         | 213 (18.4)     | <0.001*|
| Female                            | 739 (85.1)                        | 207 (71.1)                        | 946 (81.6)     |        |
| Age*                              | 49.22 (±0.47)                     | 49.93 (±0.82)                     | 49.39 (±0.41)  | 0.452* |
| **Marriage**                      |                                   |                                   |                |        |
| Single                            | 58 (6.7)                          | 22 (7.6)                          | 80 (6.9)       | 0.595* |
| Married                           | 810 (93.3)                        | 269 (92.4)                        | 1079 (93.1)    |        |
| **Comorbidity**                   |                                   |                                   |                |        |
| Hypertension                      | 190 (21.89)                       | 67 (23.02)                        | 257 (22.17)    | 0.684* |
| Diabetes                          | 79 (9.1)                          | 31 (10.65)                        | 110 (9.49)     | 0.421* |
| Cardiovascular disease            | 50 (5.76)                         | 18 (6.19)                         | 68 (5.87)      | 0.774* |
| Angiography                       | 27 (3.11)                         | 6 (2.06)                          | 33 (2.85)      | 0.420* |
| Smoking                           | 10 (1.15)                         | 1 (0.34)                          | 11 (0.95)      | 0.309* |
| Cerebral infarction               | 8 (0.92)                          | 1 (0.34)                          | 9 (0.78)       | 0.464* |
| Lung disease                      | 25 (2.88)                         | 3 (1.03)                          | 28 (2.42)      | 0.080* |
| **Risk Factor**                   |                                   |                                   |                |        |
| Participate in community meetings (yes) | 43 (5)                           | 16 (5.5)                          | 59 (5.1)       | 0.758* |
| Use of public transport           | 34 (3.9)                          | 11 (3.8)                          | 45 (3.9)       | >0.999 |
| COVID positive in family          | 9 (1)                             | 2 (0.7)                           | 11 (0.9)       | 0.740* |
| COVID positive (yes)              | 15 (1.7)                          | 5 (1.7)                           | 20 (1.7)       | >0.999 |
| **Outcomes**                      |                                   |                                   |                |        |
| Fever (yes)                       | 34 (3.9)                          | 12 (4.1)                          | 46 (4)         | 0.861* |
| Cough (yes)                       | 49 (5.6)                          | 11 (3.8)                          | 60 (5.2)       | 0.284* |
| Sputum (yes)                      | 12 (1.4)                          | 3 (1)                             | 15 (1.3)       | 0.773* |
| Shortness of breath (yes)         | 29 (3.3)                          | 7 (2.4)                           | 36 (3.1)       | 0.558* |
| Chest pain (yes)                  | 16 (1.8)                          | 4 (1.4)                           | 20 (1.7)       | 0.796* |
| Weakness and lethargy (yes)       | 23 (2.6)                          | 5 (1.7)                           | 28 (2.4)       | 0.509* |
| Muscular pain (yes)               | 28 (3.2)                          | 5 (1.7)                           | 33 (2.8)       | 0.224* |
| Runny nose (yes)                  | 12 (1.4)                          | 1 (0.3)                           | 13 (1.1)       | 0.204* |
| Sore throat (yes)                 | 27 (3.1)                          | 5 (1.7)                           | 32 (2.8)       | 0.300* |
| Vomiting nausea (yes)             | 4 (0.5)                           | 1 (0.3)                           | 5 (0.4)        | >0.999*|
| Diarrhea (yes)                    | 9 (1)                             | 2 (0.7)                           | 11 (0.9)       | 0.740* |
| Headache (yes)                    | 25 (2.9)                          | 0 (0)                             | 25 (2.2)       | 0.002* |
| Dizziness (yes)                   | 7 (0.8)                           | 0 (0)                             | 7 (0.6)        | 0.202* |
| **Outcomes**                      |                                   |                                   |                |        |
| Weight Loss (yes)                 | 2 (0.2)                           | 0 (0)                             | 2 (0.2)        | >0.999*|
| Decreased appetite (yes)          | 4 (0.5)                           | 1 (0.3)                           | 5 (0.4)        | >0.999*|
| Decreased olfactory (yes)         | 11 (1.3)                          | 2 (0.7)                           | 13 (1.1)       | 0.536* |
| Decreased taste (yes)             | 6 (0.7)                           | 2 (0.7)                           | 8 (0.7)        | >0.999*|
| Itching (yes)                     | 0 (0)                             | 0 (0)                             | 0 (0)          | NC     |
| Skin rash (yes)                   | 0 (0)                             | 0 (0)                             | 0 (0)          | NC     |
| Itching and eye irritation (yes)  | 4 (0.5)                           | 0 (0)                             | 4 (0.3)        | NC     |
| Frequent urination (yes)          | 1 (0.1)                           | 1 (0.3)                           | 2 (0.2)        | 0.439* |
| Burning urine (yes)               | 4 (0.5)                           | 0 (0)                             | 4 (0.3)        | 0.557* |
| Urinary incontinence (yes)        | 0 (0)                             | 0 (0)                             | 0 (0)          | NC     |
| Oral plague (yes)                 | 2 (0.2)                           | 0 (0)                             | 2 (0.2)        | >0.999*|
| **Drug**                          |                                   |                                   |                |        |
| Prednisolone                      | 664 (76.59)                       | 150 (51.55)                       | 814 (70.29)    | <0.001*|
| Biological drug                   | 47 (5.5)                          | 28 (9.82)                         | 75 (6.58)      | 0.013* |
| Vitamin D                         | 544 (62.67)                       | 126 (43.3)                        | 670 (57.81)    | <0.001*|
| Azathioprine                      | 125 (14.4)                        | 13 (4.47)                         | 138 (11.91)    | <0.001*|
| Methotrexate                      | 353 (40.67)                       | 122 (41.92)                       | 475 (40.98)    | 0.731* |
| ACEI                              | 23 (2.65)                         | 8 (2.75)                          | 31 (2.67)      | >0.999*|
| ARB                               | 107 (12.33)                       | 48 (16.49)                        | 155 (13.37)    | 0.074* |

*All data are expressed as No. (%) except for age.

* The chi-square test was used for the comparison.

* The Fisher exact test was used for the comparison.

* The independent t-test was used for the comparison.
| Item | COVID (+) (n=20) | COVID (-) (n=1139) | Total (n=1159) | P Value |
|------|-----------------|-------------------|----------------|---------|
| **Demographical Variable** | | | | |
| Gender | | | | |
| Male | 5 (25) | 208 (18.26) | 213 (18.4) | 0.393* |
| Female | 15 (75) | 931 (81.74) | 946 (81.6) | >0.999 |
| Age** (years) | 46.30 (±2.54) | 49.45 (±0.41) | 49.39 (±0.41) | 0.319 |
| Marriage | | | | |
| Single | 1 (5) | 79 (6.94) | 80 (6.9) | >0.999 |
| Married | 19 (95) | 1060 (93.06) | 1079 (93.1) | >0.999 |
| **Comorbidity** | | | | |
| Hypertension | 4 (20) | 253 (22.21) | 257 (22.17) | >0.999 |
| Diabetes | 1 (5) | 109 (9.57) | 110 (9.49) | >0.999 |
| Cardiovascular disease | 1 (5) | 67 (5.88) | 68 (5.87) | >0.999 |
| Angiography | 1 (5) | 32 (2.81) | 33 (2.85) | 0.422 |
| Sterting | 0 (0) | 11 (0.97) | 11 (0.95) | >0.999 |
| CABG | 0 (0) | 10 (0.88) | 10 (0.86) | >0.999 |
| Cerebral infarction | 0 (0) | 9 (0.79) | 9 (0.78) | >0.999 |
| Lung disease | 0 (0) | 28 (2.46) | 28 (2.42) | >0.999 |
| Asthma | 0 (0) | 18 (1.58) | 18 (1.55) | >0.999 |
| COPD | 0 (0) | 1 (0.09) | 1 (0.09) | >0.999 |
| Sputum | 2 (10) | 57 (5) | 59 (5.1) | 0.026 |
| Chest pain (yes) | 4 (20) | 24 (2.11) | 28 (2.4) | 0.001 |
| Weakness and lethargy (yes) | 7 (35) | 26 (2.28) | 33 (2.8) | <0.001 |
| Muscular pain (yes) | 1 (5) | 13 (1.14) | 13 (1.1) | >0.999 |
| Sore throat (yes) | 6 (30) | 26 (2.28) | 32 (2.8) | <0.001 |
| Vomiting nausea (yes) | 2 (10) | 6 (0.53) | 8 (0.7) | 0.007 |
| Diarrhea (yes) | 3 (15) | 8 (0.7) | 11 (0.9) | 0.001 |
| Headache (yes) | 6 (30) | 19 (1.67) | 25 (2.2) | <0.001 |
| Dizziness (yes) | 1 (5) | 6 (0.53) | 7 (0.6) | 0.115 |
| Weight loss (yes) | 1 (5) | 3 (0.26) | 4 (0.3) | 0.067 |
| Decreased appetite (yes) | 0 (0) | 5 (0.44) | 5 (0.4) | >0.999 |
| Decreased olfactory (yes) | 2 (10) | 11 (0.97) | 13 (1.1) | 0.02 |
| Decreased taste (yes) | 2 (10) | 6 (0.53) | 8 (0.7) | 0.007 |
| Itching (yes) | 0 (0) | 0 (0) | 0 (0) | NC |
| Skin rash (yes) | 0 (0) | 0 (0) | 0 (0) | NC |
| Itching and eye irritation (yes) | 0 (0) | 4 (0.35) | 4 (0.3) | >0.999 |
| Frequent urination (yes) | 0 (0) | 2 (0.18) | 2 (0.2) | >0.999 |
| Burning urine (yes) | 1 (5) | 3 (0.26) | 4 (0.3) | 0.0162 |
| Urinary incontinence (yes) | 0 (0) | 0 (0) | 0 (0) | NC |
| Oral plague (yes) | 0 (0) | 2 (0.18) | 2 (0.2) | >0.999 |
| **Drug** | | | | |
| Prednisolone | 12 (60) | 802 (70.47) | 814 (70.29) | 0.327 |
| Biological drug | 1 (5) | 74 (6.61) | 75 (6.58) | >0.999 |
| Vitamin D | 13 (65) | 657 (57.68) | 670 (57.81) | 0.649 |
| Azathioprine | 1 (5) | 137 (12.03) | 138 (11.91) | 0.498 |
| Methotrexate | 9 (45) | 466 (40.91) | 475 (40.98) | 0.819 |
| ACEI | 0 (0) | 31 (2.72) | 31 (2.67) | >0.999 |
| ARB | 2 (10) | 153 (13.43) | 155 (13.37) | >0.999 |

*All data are expressed as No. (%) except for age.

* The chi-square test was used for the comparison.

** The Fisher exact test was used for the comparison.

The independent t-test was used for the comparison.
The incidence of COVID-19 did not differ between patients with rheumatologic disorders had COVID-19. Receiving ARBs or ACEIs was not related to the development of COVID-19 in patients with rheumatologic disorders.

6. Conclusion
The present study demonstrated that less than 2% of patients with rheumatologic disorders had COVID-19. Receiving ARBs or ACEIs was not different among patients with or without COVID-19. Receiving hydroxychloroquine was not related to the development of COVID-19 in patients with rheumatologic disorders.

Authors’ Contributions
SS, GA, NB, MI, AS, AR, SA: study design, data gathering, data analysis, interpretation, draft preparation. MHAA, ZRM, MH, ER, HI, GAI, AS: data gathering, data analysis, interpretation, draft preparation.

Conflict of Interest Disclosures
GA serves as an editor in chief of Hospital Practices and Research. AS is an assistant editor of Hospital Practices and Research. Other authors declare that they have no conflicts of interest.

Ethical Approval
The study was approved by Baqiyatallah University of Medical Sciences, Tehran, Iran, with a code of IR.BMSUREC.1399.020.

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