COVID-19 Prevalence and Outcomes among Individuals with Rheumatoid Arthritis and Systemic Lupus Erythematosus Taking Hydroxychloroquine; A Retrospective Analysis

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Abstract:

Introduction:
The SARS-CoV-2 global pandemic has resulted in a universal search for potential treatments of Coronavirus Disease 2019 (COVID-19). Initial reports of the therapeutic potential of chloroquine (CQ) and hydroxychloroquine (HCQ) and early non-randomized non-controlled studies were followed by subsequent trials refuting such properties. The use of CQ and HCQ in diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), prompted us to examine the prevalence of COVID-19 and proposed prophylactic and therapeutic properties of HCQ in this population.

Methods:
A total of 103 patients with RA and SLE aged 18 to 75 diagnosed with COVID-19 were identified. The patients were categorized as those taking HCQ (cases) and those not on HCQ (controls) for at least 6 months. Primary (mechanical ventilation, length of stay, death) and secondary outcomes were defined, data were collected, and results were compared and statistically analyzed between cases and controls.

Results:
No statistical difference was observed in demographic features, baseline comorbidities, and medications. Primary outcomes’ statistical analysis did not reveal any differences between cases and controls. Statistical analysis of secondary outcomes revealed that cases had a statistically higher chance of being tachypneic (p 0.034). D-Dimer (p 0.017) and LDH levels (p 0.044) were found to be significantly lower in cases versus controls.

Conclusion:
This study highlights the lack of clinical prophylactic and therapeutic efficacy of HCQ against COVID-19 when taken at regular doses for patients with RA and SLE. It also shows that the prevalence of COVID-19 was similar in RA and SLE patients regardless of baseline consumption of HCQ.

Keywords: COVID-19, Hydroxychloroquine, Chloroquine, Rheumatoid arthritis, Systemic lupus erythematosus, Medications.

1. INTRODUCTION

The coronaviruses are positive-stranded RNA viruses that usually lead to mild upper respiratory tract infections without complications [1]. In the early 21st century, new species of this family, Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome coronavirus (MERS-CoV), emerged [2], causing severe respiratory disease. SARS-CoV-2, a third novel coronavirus and the causative agent of coronavirus disease 2019 (COVID-19), emerged from Wuhan, China, in late 2019 and led to an ongoing, challenging worldwide pandemic in 2020 [1]. A global attempt to develop pharmacotherapeutics and vaccines has ensued since the emergence of SARS-CoV-2. The most debated and presumed initially effective medications for COVID-19 are the antimalarial agents chloroquine (CQ) and hydroxychloroquine (HCQ).

While the anti-inflammatory and anti-malarial properties of these drugs have long been recognized, their potential use for the management of Rheumatoid Arthritis (RA) and Systemic
Lupus Erythematosus (SLE) was quite incidental [3]. Nevertheless, they now comprise a cornerstone in the management of autoimmune diseases [3, 4]. The immunomodulatory effects of these medications have been further elucidated through a variety of studies, with these medications shown to inhibit endosomal maturation by abrogating endosomal acidification resulting in inhibition of proteolysis, glycosylation, antigen presentation, and innate and adaptive immune mechanisms by the inhibition of Toll-like receptor signaling, modulation of the production of inflammatory cytokines, Interleukin-1 (IL-1), Interleukin-6 (IL-6), and Tumor Necrosis Factor-alpha (TNF-alpha) by macrophages/monocytes, and inhibition of T- and B-cell signaling [3 - 5]. Given these anti-inflammatory properties, it is hypothesized that these medications could inhibit initial viral infection, the resultant inflammatory cascade, and viral release via reduced acidification of endocytic vesicles leading to reduced viral infectivity [6 - 9]. In the case of these novel coronaviruses, glycosylation of the cell-surface receptor ACE2 seems to be important in viral docking and entry. HCQ inhibition of ACE2 glycosylation is associated with reduced infection in in vitro models and was also found to be effective not only in treating infection but also in preventing infection, highlighting the potential prophylactic use of chloroquine and HCQ in SARS-CoV-1 [10] and subsequently SARS-CoV-2 [11 - 13]. Influenced by this data and the global search of treatment for COVID-19, Gautret and colleagues reported a non-randomized clinical trial that demonstrated increased SARS-CoV-2 clearance with HCQ [14]. Despite widespread initial acceptance, several key issues with the study were raised, including a small sample size and discrepancies between the control and treatment groups, among others. Several follow-up studies by the same group as well as others reported clinical benefit [14, 15], while separate studies found no significant benefit with HCQ in COVID-19 [16 - 22].

Individuals with autoimmune disease, specifically RA and SLE, provide a unique lens by which HCQ and its effect on SARS-CoV-2 pathogenesis, infectivity, and the outcome can be evaluated. Considering controversies and the ongoing global debate regarding the efficacy and safety of chloroquine and HCQ as a prophylactic and therapeutic option for COVID-19, we proposed to examine the prophylactic and therapeutic efficacy of HCQ in individuals with RA or SLE on HCQ across the MedStar Health system and evaluate the incidence and outcomes of SARS-CoV-2 infection in this specific population.

2. METHODOLOGY

Patients diagnosed with RA or SLE, aged 18 - 75, across all inpatient and outpatient MedStar Health facilities were identified. Only those that were diagnosed with COVID-19 via a positive SARS-CoV-2 PCR assay were subsequently selected. The date range for inclusion was March 1, 2020, to June 15, 2020. Two comparison groups were subsequently made: 1) individuals actively taking HCQ at the time of the study (cases), and 2) individuals not taking HCQ at the time of the study (controls) (Fig. 1). Patients that were taking HCQ for at least 6 months, previously defined as the duration to reach a steady-state [23], were labeled as cases. Dosage, frequency, and whether HCQ was continued if admitted to the hospital were also noted. Other chronic medications, such as diabetic medications, beta-blockers, and angiotensin-converting enzyme inhibitors (ACE)/angiotensin II receptor blockers (ARBs), as well as additional immunomodulators (colchicine, belimumab, etanercept (Enbrel), methotrexate, Enbrel, sulfasalazine), were recorded.

Demographics and COVID-19 associated features including the presence of symptoms (fever, cough, sputum production, shortness of breath, tachypnea, tachycardia, diarrhea, nausea, and vomiting) and medical comorbidities (smoking, asthma, hypertension, hyperlipidemia, COPD, CKD, obesity, diabetes mellitus, etc.) were analyzed. A respiratory rate of greater than 20 breaths per minute was considered tachypnea, and a heart rate of greater than 100 beats per minute was considered tachycardia. To eliminate possible charting errors, we considered 2 or more recordings of each tachycardia and tachypnea to be counted as the true presence of these symptoms. The complete list of medical comorbidities and symptoms is given in Table 1, respectively.

Other COVID-19 and patient-associated factors were categorized into primary and secondary outcomes. We defined primary outcomes as the need for mechanical ventilation, hospital length of stay, and death. Secondary outcomes were defined as symptoms and signs upon presentation, radiological findings, primary laboratory data, and other COVID-19 associated complications such as admission to hospital, admission to intensive care unit, hypoxia, acute kidney injury, elevation in liver enzymes, and acute respiratory distress syndrome. Radiological findings were further categorized into three groups of bilateral infiltrates, bilateral opacities, and ground-glass opacities. Hypoxia was defined as the need for a nasal cannula or a SpO2 less than 92%, whereas sepsis was defined by a qSOFA score equal to or greater than 2. Statistical analyses were performed using mean and standard deviations for continuous variables and frequency and percentages for categorical variables. Comparisons of the means of the two groups, cases, and controls, were made using two samples t-test. Interquartile range was used to determine the spread of data points. Proportions of the two groups were compared using the chi-square test or Fisher’s exact test. Some p-values were not performed due to small sample sizes.

3. RESULTS

Among the 123 patients that were identified, 20 patients failed to either meet the inclusion criteria or were falsely included and were subsequently excluded from the study (Fig. 1). A total of 103 SARS-CoV-2 PCR positive RA and/or SLE patients were subsequently identified and selected for this retrospective observational study. After data collection and appropriate categorization, patient-specific features such as demographics, baseline medications, signs and symptoms on presentation, and primary and secondary outcomes were compared and analyzed between cases and controls. Overall, the study population included 84 (81.6%) females and 19 (18.4%) males. There were 40 (38.8%) and 63 (61.2%) patients in the cases and control groups, respectively. The mean age of cases was 53.3 years (SD: 15.9), comprised of 17 (42.5%)
patients with RA, 22 (55%) patients with SLE, and 1 (2.5%) patient with both RA and SLE, while the mean age of controls was 64.6 years (SD: 14.3), comprised of 53 (84.1%) patients with RA and 10 (15.9%) patients with SLE (Table 1). Medications such as beta-blockers, angiotensin-converting enzyme inhibitors, and diabetic medications were also analyzed without any meaningful trend or difference between the two groups (Table 1). RA and SLE-specific medications other than HCQ were also reviewed and analyzed. Steroids and methotrexate comprised the most frequently utilized adjunctive therapeutics, while other adjunctive agents included sulfasalazine, etanercept, colchicine, and belimumab. Cases were more likely to be on belimumab and less likely to be on methotrexate with p values of 0.021 and less than 0.001, respectively.

Primary outcomes, as defined in the methods section, were compared and analyzed for any statistical difference between the cases and control groups. No statistically significant differences were identified for primary outcomes (Table 2).

Chest radiographs and computed tomography from the day of presentation were analyzed with findings categorized into three groups, including bilateral infiltrates, bilateral opacities, and ground-glass opacity compared between cases and controls. There were no significant differences observed in the cases versus controls. Laboratory diagnostics that have been previously associated with COVID-19 infection, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), creatinine phosphokinase (CPK), D-dimer, and liver enzymes [24], were also compared. Notable findings included a statistically significant higher rate of tachypnea (p 0.034), as well as higher D-dimer (2.5 mcg/ml v. 0.9 mcg/ml; p 0.017) and LDH levels (410 units/L v. 295.5 units/L; p 0.044) in controls compared to cases (Table 3). Analysis of other secondary outcome variables failed to show any statistically significant differences between the cases and controls.

![Diagram](https://via.placeholder.com/150?text=Fig. (1). Comparison of study groups.)

**Table 1. Demographical data for HCQ and control groups.**

|               | All          | Cases         | Control       | P Value |
|---------------|--------------|---------------|---------------|---------|
| Sex           | Female       | 84 (81.6%)    | 37 (92.5%)    | 47 (74.6%) | 0.022 |
|               | Male         | 19 (18.4%)    | 3 (7.5%)      | 16 (25.4%) |       |
| Age           | Mean (SD)    | 60.2 (15.9)   | 53.3 (15.9)   | 64.6 (14.3) | <0.001|
| SLE, RA       | RA           | 70 (68%)      | 17 (42.5%)    | 53 (84.1%) | <0.001|
|               | SLE          | 32 (31.1%)    | 22 (55%)      | 10 (15.9%) |       |
|               | SLE & RA     | 1 (1%)        | 1 (2.5%)      | 0 (0%)    |       |
| Race          | African American | 58 (58%)  | 18 (45%)      | 40 (66.7%) | 0.029 |
|               | Other        | 22 (22%)      | 14 (35%)      | 8 (13.3%) |       |
|               | White        | 20 (20%)      | 8 (20%)       | 12 (20%)  |       |

SLE, Systemic Lupus Erythematosus, RA, Rheumatoid Arthritis.
### Table 2. Comorbidities data for HCQ and control groups.

|                | All       | Cases     | Control    | P Value |
|----------------|-----------|-----------|------------|---------|
| Smoker         | Yes       | 2 (1.9%)  | 1 (2.5%)   | 1       |
|                | No        | 101 (98.1%) | 39 (97.5%) | 62 (98.4%) | -       |
| Asthma         | Yes       | 12 (11.7%) | 6 (15%)    | 6 (9.5%) | 0.53    |
|                | No        | 91 (88.3%) | 34 (85%)   | 57 (90.5%) | -       |
| HTN            | Yes       | 56 (54.4%) | 17 (42.5%) | 39 (61.9%) | 0.054   |
|                | No        | 47 (45.6%) | 23 (57.5%) | 24 (38.1%) | -       |
| Hyperlipidemia | Yes       | 6 (5.8%)   | 4 (10%)    | 2 (3.2%) | 0.204   |
|                | No        | 97 (94.2%) | 36 (90%)   | 61 (96.8%) | -       |
| COPD           | Yes       | 5 (4.9%)   | 1 (2.5%)   | 4 (6.3%) | 0.646   |
|                | No        | 98 (95.1%) | 39 (97.5%) | 59 (93.7%) | -       |
| CHF            | Yes       | 10 (9.7%)  | 1 (2.5%)   | 9 (14.3%) | 0.084   |
|                | No        | 93 (90.3%) | 39 (97.5%) | 54 (85.7%) | -       |
| Obesity        | Yes       | 33 (32%)   | 13 (32.5%) | 20 (31.7%) | 0.936   |
|                | No        | 70 (68%)   | 27 (67.5%) | 43 (68.3%) | -       |
| Malignancy     | Yes       | 4 (3.9%)   | 3 (7.5%)   | 1 (1.6%) | 0.296   |
|                | No        | 99 (96.1%) | 37 (92.5%) | 62 (98.4%) | -       |
| DM             | Yes       | 28 (27.2%) | 12 (30%)   | 16 (25.4%) | 0.609   |
|                | No        | 75 (72.8%) | 28 (70%)   | 47 (74.6%) | -       |
| GERD           | Yes       | 5 (4.9%)   | 3 (7.5%)   | 2 (3.2%) | 0.374   |
|                | No        | 98 (95.1%) | 37 (92.5%) | 61 (96.8%) | -       |
| Depression     | Yes       | 3 (2.9%)   | 1 (2.5%)   | 2 (3.2%) | 1       |
|                | No        | 100 (97.1%) | 39 (97.5%) | 61 (96.8%) | -       |
| Fibromyalgia   | Yes       | 3 (2.9%)   | 0 (0%)     | 3 (4.8%) | 0.28    |
|                | No        | 100 (97.1%) | 40 (100%)  | 60 (95.2%) | -       |
| Myelodysplastic syndrome | Yes | 1 (1%) | 0 (0%) | 1 (1.6%) | 1 |
|                | No        | 102 (99%) | 40 (100%)  | 62 (98.4%) | -       |
| DVT            | Yes       | 4 (3.9%)   | 2 (5%)     | 2 (3.2%) | 0.641   |
|                | No        | 99 (96.1%) | 38 (95%)   | 61 (96.8%) | -       |
| Eczema         | Yes       | 1 (1%)     | 0 (0%)     | 1 (1.6%) | 1       |
|                | No        | 102 (99%) | 40 (100%)  | 62 (98.4%) | -       |
| RLD            | Yes       | 1 (1%)     | 0 (0%)     | 1 (1.6%) | 1       |
|                | No        | 102 (99%) | 40 (100%)  | 62 (98.4%) | -       |
| CVA            | Yes       | 2 (1.9%)   | 0 (0%)     | 2 (3.2%) | 0.52    |
|                | No        | 101 (98.1%) | 40 (100%)  | 61 (96.8%) | -       |
| Hypothyroidism | Yes       | 7 (6.8%)   | 3 (7.5%)   | 4 (6.3%) | 1       |
|                | No        | 96 (93.2%) | 37 (92.5%) | 59 (93.7%) | -       |
| Sicca          | Yes       | 1 (1%)     | 1 (2.5%)   | 0 (0%) | 0.388   |
|                | No        | 102 (99%) | 39 (97.5%) | 63 (100%) | -       |
| IBS            | Yes       | 1 (1%)     | 1 (2.5%)   | 0 (0%) | 0.388   |
|                | No        | 102 (99%) | 39 (97.5%) | 63 (100%) | -       |
| CAD            | Yes       | 5 (4.9%)   | 0 (0%)     | 5 (7.9%) | 0.154   |
|                | No        | 98 (95.1%) | 40 (100%)  | 58 (92.1%) | -       |
| Secondary Adrenal insufficiency | Yes | 1 (1%) | 1 (2.5%) | 0 (0%) | 0.388   |
|                | No        | 102 (99%) | 39 (97.5%) | 63 (100%) | -       |
| Hyperparathyroidism | Yes | 1 (1%) | 1 (2.5%) | 0 (0%) | 0.388 |
|                | No        | 102 (99%) | 39 (97.5%) | 63 (100%) | -       |
| Pregnancy      | Yes       | 0 (0%)     | 0 (0%)     | 0 (0%) | 1       |
|                | No        | 103 (100%) | 40 (100%)  | 63 (100%) | -       |
Table 3. Baseline medication data for HCQ and control groups.

| Medication                  | Cases | Control | P Value |
|-----------------------------|-------|---------|---------|
| Diabetic Medications        |       |         |         |
| -                           |       |         |         |
| Yes                         | 24 (23.3%) | 8 (20%) | 16 (25.4%) | 0.528 |
| No                          | 79 (76.7%) | 32 (80%) | 47 (74.6%) | -     |
| Beta blockers               |       |         |         |
| -                           |       |         |         |
| Yes                         | 27 (26.2%) | 9 (22.5%) | 18 (28.6%) | 0.495 |
| No                          | 76 (73.8%) | 31 (77.5%) | 45 (71.4%) | -     |
| ACE ARB                     |       |         |         |
| -                           |       |         |         |
| Yes                         | 35 (34.3%) | 11 (28.2%) | 24 (38.1%) | 0.307 |
| No                          | 67 (65.7%) | 28 (71.8%) | 39 (61.9%) | -     |
| Colchicine                  |       |         |         |
| -                           |       |         |         |
| Yes                         | 3 (2.9%) | 3 (7.5%) | 0 (0%) | 0.056 |
| No                          | 100 (97.1%) | 37 (92.5%) | 63 (100%) | -     |
| Belimumab                   |       |         |         |
| -                           |       |         |         |
| Yes                         | 4 (3.9%) | 4 (10%) | 0 (0%) | 0.021 |
| No                          | 99 (96.1%) | 36 (90%) | 63 (100%) | -     |
| Steroids                    |       |         |         |
| -                           |       |         |         |
| Yes                         | 22 (21.4%) | 11 (27.5%) | 11 (17.5%) | 0.226 |
| No                          | 81 (78.6%) | 29 (72.5%) | 52 (82.5%) | -     |
| Etanercept                  |       |         |         |
| -                           |       |         |         |
| Yes                         | 5 (4.9%) | 2 (5%) | 3 (4.8%) | 1     |
| No                          | 98 (95.1%) | 38 (95%) | 60 (95.2%) | -     |
| Methotrexate                |       |         |         |
| -                           |       |         |         |
| Yes                         | 23 (22.3%) | 2 (5%) | 21 (33.3%) | < 0.001 |
| No                          | 80 (77.7%) | 38 (95%) | 42 (66.7%) | -     |
| Sulfasalazine               |       |         |         |
| -                           |       |         |         |
| Yes                         | 3 (2.9%) | 2 (5%) | 1 (1.6%) | 0.558 |
| No                          | 100 (97.1%) | 38 (95%) | 62 (98.4%) | -     |

ACE, Angiotensin-Converting Enzyme inhibitor; ARB, Angiotensin II Receptor Blocker.

4. DISCUSSION

Chloroquine derivatives have been successfully used as anti-malarials as well as in the management of RA and SLE. Their proposed yet controversial, *in vitro* antiviral properties sparked a global debate during the COVID-19 pandemic, with several early studies claiming therapeutic and prophylactic properties of these medications, specifically CQ and HCQ, against SARS-CoV-2 [11 - 14]. These studies were mostly small, non-randomized, and lacked strong methodology. Nevertheless, they gained media attention in the light of this conflicting data and the significant side effects, the HCQ arm in the SOLIDARITY [35] trial by World Health Organization (WHO) was suspended due to safety concerns raised by Mehra et al. [36]. However, this study was later retracted due to concerns for suspicious unvalidated data [37]. This was followed by suspension of the HCQ arm in the RECOVERY trial [38] due to lack of efficacy, and subsequently by the WHO and National Institute of Health [25].

In our observational study, the number of cases was about two-thirds of controls, and they tended to be younger, although the selection process was completely randomized based on the presence of COVID-19 infection in patients with RA and SLE and taking HCQ at baseline. Despite the average age discrepancy between the two, both cases and controls demonstrated a similar demographic distribution and prevalence of medical comorbidities; therefore, we believe that the possibility of biased selection is very low. Our study failed to show any statistically significant differences in the primary outcomes, including hospitalization, mechanical ventilation, and death, between the cases and controls (Table 2). Among...
secondary outcomes, tachypnea, D-Dimer, and LDH were found to have significant differences between the cases and controls (Table 3), with higher rates or levels more likely to be associated with those not taking HCQ at baseline (controls). The lower levels of LDH and D-Dimer in cases, which are considered nonspecific markers of inflammation, can be explained by the anti-inflammatory properties of HCQ [4], which have been known and described. Theoretically, less inflammation in the body and specifically less inflammation of the pulmonary system may also explain a lower rate of tachypnea in individuals taking HCQ at baseline (cases). However, limitations to such findings are the multifactorial nature of tachypnea (e.g., pain, fever, anxiety, anemia, infection, etc.) and the examiner-dependent nature of this parameter. Furthermore, the significance of the elevated respiratory rate and elevated inflammatory markers in those not taking HCQ remains unclear, specifically given the lack of differences in the primary outcomes, including mechanical ventilation, hospital length of stay, and death. Cases were more likely to be on belimumab with a possible more potent suppression of the immune system at baseline; however, it is unclear if it directly affected the primary and secondary outcomes of COVID-19 in patients in our study, considering our small sample size. Although methotrexate’s anti-inflammatory properties could have potentially played a role and mask the disease severity and potentially affect primary outcomes, we believe that is less likely as the anti-inflammatory markers were higher in controls compared to cases, indicating a higher inflammatory state in the controls (who were more likely to be on methotrexate) compared to cases.

Several reports have been published on outcomes of COVID-19 in patients with SLE, each failing to demonstrate evidence of a prophylactic or therapeutic role for HCQ [16 - 22], which is similar to the findings in our study. The report from the COVID-19 Global Rheumatology Alliance by Gianfrancesco et al. [26] highlighted the incidence of COVID-19 in individuals with rheumatic disease, including RA and SLE, among others refuting prior claims that noted an absence of COVID-19 in individuals with the underlying rheumatologic disease taking HCQ [39]. König and colleagues subsequently published a report on 80 SLE patients infected with SARS-CoV-2 and demonstrated similar rates of COVID-19 infection in HCQ users and non-users [27]. A French case series reported on 17 patients with SLE infected with SARS-CoV-2, of which 76% developed pneumonia and more highlighted an increased probability of severe COVID-19 pneumonia especially in those with underlying comorbidities, such as chronic kidney disease and obesity. All patients in this study were taking HCQ for at least 6 months, with 65% taking HCQ at 400 mg daily dose with a median HCQ blood concentration of 648 ng/mL. The majority of patients (71%) were also taking maintenance prednisone (no more than 10 mg daily). Nevertheless, 82% were hospitalized with 41% admitted to intensive care unit, and 35% requiring mechanical ventilation [28]. Taken together, these reports highlighted lack of evidence for prophylactic and therapeutic properties of HCQ.

One possible explanation for the lack of efficacy of HCQ, specifically in those with underlying RA or SLE, may relate to epigenetic modifications, with resultant effects on gene transcription and protein translation. Individuals with RA and SLE have demonstrated significantly altered methylation patterns in the promoter regions of multiple genes. Intriguingly, individuals with SLE demonstrated hypomethylation of ACE2, the functional receptor for SARS-CoV-2 [40], whereas individuals with RA demonstrated hypomethylation of IL6 [41], a protein intricately involved in the “cytokine storm” of SARS-CoV-2, with concomitant elevations of both proteins, respectively, a feature that may be further abrogated by the severity of the underlying SLE or RA. A systematic review and meta-analysis revealed an increased risk of COVID-19 in patients with underlying autoimmune diseases and that glucocorticoid use was significantly associated with a higher risk of infection [42]. This increased risk of infection is hypothesized to be related to the suppressed and partially dysregulated immune system in those with underlying autoimmune/ rheumatic disease, their concomitant epigenetic modifications and elevated inflammatory state, and the concomitant use of immunosuppressants, all of which may impair the normal immune response. It is also noteworthy that regular steroid use in patients without respiratory failure, as described in the RECOVERY trial, was not beneficial and possibly associated with adverse outcomes [38]. Our study, however, failed to demonstrate such an association, specifically with respect to steroid use, though the sample size and frequency of steroid use were substantially low (Table 1). Similar to the increasing number of reports demonstrating lack of efficacy of HCQ in preventing or treating COVID-19, a recent systematic review demonstrated no short-term mortality benefit in patients who received HCQ monotherapy and increased mortality in those on combination therapy with azithromycin [43].

CONCLUSION

While the potential prophylactic and therapeutic properties of CQ and HCQ were originally touted by several studies during the early months of the COVID-19 pandemic, subsequent studies including randomized clinical trials and meta-analyses failed to prove such therapeutic potential. Our study, while limited due to its retrospective and observational nature and fairly small sample size, supports emerging data that HCQ at regular doses used in the management of patients with RA or SLE has no prophylactic or therapeutic benefit. Considering the underlying predisposition for inflammation and epigenetic modifications in RA and SLE, as well as increased vulnerability to infection, our study revealed that the prevalence of infection with SARS-CoV-2 was similar in RA and SLE patients with no difference with respect to baseline use of HCQ. Although tachypnea and elevated levels of LDH and D-Dimer were statistically more frequent in controls compared to cases, no difference was observed in primary outcomes such as mechanical ventilation and death among the two groups.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was performed based on the MedStar IRB
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approval however no ethics committee was required as study was only performed by chart review and names of patients were blinded for confidentiality reasons.

HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was taken from all the participants when they were enrolled.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author [A.M] upon reasonable request.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

REFERENCES

[1] Paules CI, Marston HD, Fauci AS. Coronavirus infections-more than just the common cold. JAMA 2020; 323(8): 707-8.
[2] de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: Recent insights into emerging coronaviruses. Nat Rev Microbiol 2016; 14(8): 523-34. [http://dx.doi.org/10.1038/nrmicro.2016.81] [PMID: 27344959]
[3] Ben-Zvi I, Kivity S, Langevitz P, Shoenfeld Y. Hydroxychloroquine: From malaria to autoimmunity. Clin Rev Allergy Immunol 2012; 42(2): 145-53. [http://dx.doi.org/10.1007/s12016-010-8243-x] [PMID: 21221847]
[4] Hu C, Lu L, Wan JP, Wen C. The pharmacological mechanisms and therapeutic activities of hydroxychloroquine in rheumatic and related diseases. Curr Med Chem 2017; 24(20): 2241-9. [http://dx.doi.org/10.2174/092986732466170316115938] [PMID: 28302011]
[5] Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: Implications for rheumatology. Nat Rev Rheumatol 2020; 16(3): 155-66. [http://dx.doi.org/10.1038/s41584-020-0372-x] [PMID: 32034323]
[6] Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: An old drug against today’s diseases? Lancet Infect Dis 2005; 5(11): 722-7. [http://dx.doi.org/10.1016/S1473-3099(05)00806-5] [PMID: 14952603]
[7] Planteau D, Koudriavtseva T. Current and future use of chloroquine and hydroxychloroquine in infectious, immune, neoplastic, and neurological diseases: A mini-review. Clin Drug Invest 2018; 38(8): 633-71. [http://dx.doi.org/10.1007/s40261-018-0656-y] [PMID: 29737455]
[8] Keyaerts E, Li S, Vijgen L, et al. Antiviral activity of chloroquine against human coronavirus OC43 infection in newborn mice. Antimicrob Agents Chemother 2009; 53(8): 3416-21. [http://dx.doi.org/10.1128/AAC.01509-08] [PMID: 19506054]
[9] Keyaerts E, Vijgen L, Maes P, Neyts J, Van Ranst M. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun 2004; 323(1): 264-8. [http://dx.doi.org/10.1016/j.bbrc.2004.08.085] [PMID: 15351731]
[10] Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005; 2: 69. [http://dx.doi.org/10.1186/1743-422X-2-69] [PMID: 16153138]
[11] Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different clinical samples. JAMA 2020; 323(18): 1843-4. [http://dx.doi.org/10.1001/jama.2020.3786] [PMID: 32159755]
[12] Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov 2020; 6: 16. [http://dx.doi.org/10.1038/s41421-020-0156-0]
[13] Yao X, Ye F, Zhang M, et al. In Vivo antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In: Clin Infect Dis Official Publ Infect Dis Soc Am. 2020. [http://dx.doi.org/10.1093/cid/ciaa237]
[14] Gauthier P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020; 56(1):105949. [http://dx.doi.org/10.1016/j.ijantimicag.2020.105949] [PMID: 32205104]
[15] Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020; 14(1): 72-3. [http://dx.doi.org/10.5582/bst.2020.01047] [PMID: 32974550]
[16] Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial Medrxiv 2020. [http://dx.doi.org/10.1101/2020.03.22.20040758]
[17] Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect 2020; 50(4): 384. [http://dx.doi.org/10.1016/j.medmal.2020.03.006] [PMID: 32240719]
[18] Mahévas M, Tran VT, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: Results of a study using routinely collected data to emulate a target trial Medrxiv 2020. [http://dx.doi.org/10.1101/2020.04.10.20060699]
[19] Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with COVID-19: An open-label, randomized, controlled trial Medrxiv 2020. [http://dx.doi.org/10.1101/2020.04.06.20065588]
[20] Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19 Medrxiv 2020. [http://dx.doi.org/10.1101/2020.04.16.2005920]
[21] Geleris J, Sun Y, Piatt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med 2020; 382(25): 2411-8. [http://dx.doi.org/10.1056/NEJMoa2012410] [PMID: 32379955]
[22] Cavalcanti AB, Zampieri FG, Rosa RG, et al. Coalition Covid-19 Brazil Investigators. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med 2020; 383(21): 2041-52. [http://dx.doi.org/10.1056/NEJMoa2019014] [PMID: 32706953]
[23] Carmichael SJ, Charles B, Tett SE. Population pharmacokinetics of hydroxychloroquine in patients with rheumatoid arthritis. Ther Drug Monit 2005; 25(6): 671-81. [http://dx.doi.org/10.1097/00007691-200312000-00006] [PMID: 14639053]
[24] Zeng F, Huang Y, Guo Y, et al. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. Int J Infect Dis 2020; 96: 467-74. [http://dx.doi.org/10.1016/j.ijid.2020.05.055] [PMID: 32425643]
[25] Sattui SE, Liew JW, Graef ER, et al. Swinging the pendulum: lessons learned from public discourse concerning hydroxychloroquine and COVID-19. Expert Rev Clin Immunol 2020. [http://dx.doi.org/10.1080/1744666X.2020.1792778]
[26] Gianfrancesco MA, Hyrlik KL, Gossec L, et al. COVID-19 global rheumatology alliance steering committee. Rheumatic disease and COVID-19: Initial data from the COVID-19 Global Rheumatology
Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: A randomized clinical trial. JAMA Netw Open 2020; 3(4):e208857 [http://dx.doi.org/10.1001/jamanetworkopen.2020.8857] [PMID: 32330277]

Pan H, Peto R, Henao Restrepo. Repurposed antiviral drugs for Covid-19 — interim who solidarity trial results. N Engl J Med 2020; 384:497-511.

Mehra MR, Desai SS, Ruschitzka F, Patel AN. RETRACTED: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: A multinational registry analysis. Lancet 2020;S0140-6736(20)31180-6 [http://dx.doi.org/10.1016/S0140-6736(20)31180-6] [PMID: 32450107]

Mehra MR, Ruschitzka F, Patel AN. Retraction-Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: A multinational registry analysis. Lancet 2020; 395(10240): 1820 [http://dx.doi.org/10.1016/S0140-6736(20)31324-6] [PMID: 32511943]

Horby P, Lim W S, Emberson J R. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 2020; 384: 693-704.

Joshi B, Wiwanitkit V. SLE, hydroxychloroquine and no SLE patients with COVID-19: A comment. Ann Rheum Dis 2020; 79(6): e61-1. [http://dx.doi.org/10.1136/annrheumdis-2020-217506] [PMID: 32925787]

Sawalha AH, Zhao M, Coit P, Lu Q. Epigenetic dysregulation of ACE2 and interferon-regulated genes might suggest increased COVID-19 susceptibility and severity in lupus patients. Clin Immunol 2020; 215:108410 [http://dx.doi.org/10.1016/j.clim.2020.108410] [PMID: 32276140]

Nile CJ, Read RC, Akil M, Duff GW, Wilson AG. Methylation status of a single CpG site in the IL6 promoter is related to IL6 messenger RNA levels and rheumatoid arthritis. Arthritis Rheum 2008; 58(9): 2686-93. [http://dx.doi.org/10.1002/art.23758] [PMID: 18759290]

Akiyama S, Hambidi S, Mici D, Sakuraba A. Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: A systematic review and meta-analysis. Ann Rheum Dis 2020; 218946(2020) [http://dx.doi.org/10.1136/annrheumdis-2020-218946]

Kashour Z, Bizas M, Garbati M A, et al. Efficacy of chloroquine or hydroxychloroquine in COVID-19 patients: A systematic review and meta-analysis. J Antimicrob Chemother 2020; 403(2020) [http://dx.doi.org/10.1093/jac/dkaa403]