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Continuous hydroxychloroquine or colchicine therapy does not prevent infection with SARS-CoV-2: Insights from a large healthcare database analysis

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ABSTRACT

Background: Some disease-modifying agents commonly used to treat patients with rheumatic diseases/auto-immune disorders, such as hydroxychloroquine and colchicine, are under investigation as potential therapies for the “coronavirus disease 2019” (COVID-19). However, the role of such agents as prophylactic tools is still not clear.

Methods: This is a retrospective study based on a large healthcare computerized database including all patients that were screened for the “Severe Acute Respiratory Syndrome Coronavirus type 2” (SARS-CoV-2) in the study period from February 23rd 2020 to March 31st 2020. A comparison was conducted between subjects tested positive for SARS-CoV-2 and those found negative in terms of rate of administration of hydroxychloroquine/colchicine therapy.

Results: An overall sample of 14,520 subjects were screened for SARS-CoV-2 infection and 1317 resulted positive. No significant difference was found in terms of rates of usage of hydroxychloroquine or colchicine between those who were found positive for SARS-CoV-2 and those who were found negative (0.23% versus 0.25% for hydroxychloroquine, and 0.53% versus 0.48% for colchicine, respectively).

Conclusion: These findings raise doubts regarding the protective role of these medications in the battle against SARS-CoV-2 infection.

1. Introduction

“Coronavirus disease 2019” (COVID-19) is a generally mild but sometimes severe and potentially even life-threatening infection caused by the “Severe Acute Respiratory Syndrome Coronavirus type 2” (SARS-CoV-2), previously known as “2019 novel coronavirus” (2019-nCoV). Since late December 2019, the SARS-CoV-2 has quickly spread out from its first epicenter, the city of Wuhan, Hubei Province, People's Republic of China [1], and has shortly become a pandemic [2]. Epidemiological data are mainly available for those countries most hardly hit by COVID-19, such as People's Republic of China [3–9], Italy [10] and the USA [11–13]. More limited information is available for countries like Israel. On the other hand, these surveys mainly deal with clinical characteristics of COVID-19 patients, in terms of related risk factors or

underlying co-morbidities, whereas unsatisfactory information is provided regarding the therapeutic interventions adopted. Furthermore, these studies are mostly clinical reports, case-series, or are designed as specific cohort studies targeting specific populations, and are not conducted at the level of entire communities, for example exploiting computerized clinical records and similar “real-world data” [14]. A notable exception is represented by the report published by the Chinese Center for Disease Control and Prevention, that analyzed the characteristics of 72,314 COVID-19 patients, even though only 62% of the entire sample consisted of confirmed cases [3]. Thus, currently available data do not enable to address some crucial research questions, especially in terms of therapeutics [15,16].

Currently, no effective vaccines or specific drugs exist that can be used to prevent or counteract/mitigate the burden of COVID-19 and so

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Table 1
Demographics and co-morbidities of the study population stratified according to SARS-CoV-2 positive and negative subjects.

	SARS-CoV-2		All	P-value
	Positive	Negative	N = 14,520	
	n = 1317	n = 13,203		
Sex, female, n (%)	529 (40.2%)	7111 (46.1%)	7640 (47.4%)	<0.001
Age (years), mean (SD)	40.6 (19.1)	37.0 (19.1)	37.3 (19.1)	<0.001
Socioeconomic status: Low	27.9%	12.7%	14.1%	<0.001
Medium	44.9%	50%	49.5%	
High	27.2%	37.3%	36.4%	
BMI (kg/m ²), %: <25	45.7%	52.6%	52.0%	< 0.001
25–30	29.1%	24.7%	25.1%	
30–35	14.1%	10%	10.4%	
> 35	5.2%	4.6%	4.6%	
IHD, n (%)	40 (3%)	331 (2.5%)	371 (2.6%)	0.245
DM, n (%)	115 (8.7%)	642 (4.9%)	757 (5.2%)	<0.001
CKD, n (%)	104 (7.9%)	823 (6.2%)	927 (6.4%)	0.019
Hypertension	185 (14%)	1445 (10.9%)	1630 (11.2%)	0.001
Chronic use of hydroxychloroquine prior to COVID-19 outbreak	3 (0.23%)	33 (0.25%)	36 (0.25%)	0.877
Chronic use of colchicine prior to COVID-19 outbreak	7 (0.53%)	64 (0.48%)	71 (5%)	0.817

BMI-body mass index, IHD- ischemic heart disease, DM – diabetes mellitus, CKD- chronic kidney disease.

far countries have adopted behavioral, non-pharmacological intervention (NPI)-based strategies, enforcing social distancing, self-isolation, quarantine and even lockdown of entire territories and communities. Since NPIs are resource-consuming, being unfeasible and unsustainable for long periods in the western countries and given that the discovery of new vaccine candidates or new chemical/molecular entities (NCEs/NMEs), the design and the implementation of randomized controlled trials (RCTs) are time-consuming procedures, some scholars are attempting to repurpose already existing compounds.

Hydroxychloroquine is an anti-malarial drug, utilized also for the treatment of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and porphyria cutanea tarda patient [17]. Colchicine is utilized for the treatment and management of patients with gout and Behçet's disease and for the prevention of pericarditis and familial Mediterranean fever (FMF), being preferred over other possible therapeutic options, such as non-steroidal anti-inflammatory drugs (NSAIDs) or steroids [18].

Contrasting findings have been reported in the existing scholarly literature concerning potential anti-viral effects of these compounds. As such, in this study, we investigated whether a chronic baseline use of anti-inflammatory medications (namely, hydroxychloroquine and colchicine) could provide a potentially beneficial effect in preventing or, at least partially, mitigating the burden of the SARS-CoV-2 infection. Therefore, for this purpose, we utilized a large Israeli healthcare database.

2. Material and methods

2.1. Setting and data source

Maccabi Health Services (MHS) is the second largest sick fund in Israel, insuring and providing care to 2.3 million persons. Since 1995, MHS has maintained a computerized database which includes all physicians' visits, diagnoses, hospitalizations, medications dispensed, all laboratory tests performed and other diagnostic procedures. In the present analysis, we included all individuals tested for SARS-CoV-2. The study protocol was in-depth reviewed and approved by MHS's Research Ethics Board.

2.2. Study population

In Israel, the first COVID-19 case was confirmed on February 21st 2020 and, since then, the epidemic is on the rise. Using the MHS

database, we identified all COVID-19 confirmed cases, defined as positive for SARS-CoV-2 according to the result of the real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR)-based assay of nasal and throat swab specimens between February 23rd 2020 (index case in the MHS database) and March 31st 2020. Subjects negative for SARS-CoV-2 were used as the control group. Criteria for testing were established according to the guidelines published by the Israeli Ministry of Health ("Guidelines for coping with the novel coronavirus", 2020, Ministry of Health, Israel) [17], which included an acute febrile illness or respiratory symptoms (cough or shortness of breath) in people returning from abroad travels or who were in close contact with a confirmed or probable COVID-19 case in the last 14 days. The MHS database was also extensively mined to collect all available information on demographics, the most recent documented body mass index (BMI), medical conditions, dispensed and prescribed hydroxychloroquine and colchicine between January 1st 2020 and the date of first SARS-COV-2 test. Furthermore, the socioeconomic status (SES) was computed, defined according to the poverty index of each member as specified during the 2008 National Census, which takes into account several parameters, including household income, education, crowding, material conditions, and car ownership, among others.

2.3. Statistical analysis

After visually inspecting data for potential outliers, descriptive statistics was carried out. Continuous data were expressed as mean \pm standard deviation and categorical parameters were computed as percentages, where appropriate. Based on the normality of data distribution, Student's *t*-test (or its non-parametric version) and chi-squared test were conducted to compare parameters between COVID-19 positive and negative individuals. Figures with *p*-values equal to or less than 0.05 were considered statistically significant. Statistical analyses were carried out by means of the commercial software "Statistical Package for Social Sciences" (SPSS for Windows, version 24.0, IBM Corp., Armonk, NY, USA).

3. Results

An overall sample of 14,520 subjects were screened for COVID-19. Their characteristics are summarized in Table 1. Mean age of the cohort was 37.3 ± 19.1 years with a slight male predominance (52.6%). Only 1317 (9.07%) resulted positive for COVID-19, approximately 60% of which were males (*p*-value <.001). The age group distribution was

similar among the subjects positive for COVID-19 compared to controls even though the mean age was higher in cases (40.6 ± 19.1 years) versus controls (average age 37.0 ± 19.1 years; p -value $< .001$). The BMI group distribution differed among cases and controls (p -value $< .001$), with the former ones reporting more overweight and obesity than the latter ones. The frequency of all co-morbidities was higher among positive subjects: in more detail, the prevalence rates of diabetes mellitus (DM) (8.7% versus 4.9%, $p < .001$), chronic kidney disease (7.9% versus 6.2%, $p = .019$) and hypertension (14% versus 10.9%, $p = .001$) were found to be statistically significant and higher among the COVID-19 positive patients. Ischemic heart disease (IHD), instead, was reported in similar percentages by cases and controls (3% versus 2.5%, respectively, $p = .245$). Of note, more cases than controls (27.9% versus 12.7%, p -value $< .001$) lived in households that were of low SES.

Concerning the baseline treatment, hydroxychloroquine and colchicine were prescribed to subjects with SARS-CoV-2 infection compared to those without in rate of 0.23% versus 0.25% ($p = .877$) and 0.53% versus 0.48% ($p = .817$) of the populations, respectively (Table 1).

4. Discussion

In the present study, we have utilized “real-world data” to explore the associations between subjects positive for SARS-COV-2, different underlying co-morbidities and medications, which were not administered for anti-viral treatment purposes. We demonstrated that some underlying co-morbidities (DM, hypertension, and CKD, but not IHD), high BMI and male gender were associated with a higher susceptibility of contracting SARS-CoV-2 infection.

Our results are in line with a recently published comprehensive meta-analysis pooling together 19 studies (18 from mainland China and one from Australia), the overall sample of which consisted only of confirmed patients according to the procedure of RT-PCR testing [5]. More than half (56%) of the patients were males and the major underlying co-morbidities were hypertension (18.6%), cardiovascular disease (14.4%) and DM (11.9%). In a population-based study evaluating the clinical characteristics of 1482 patients hospitalized with COVID-19 in the USA [19] the majority of patients were males (54.4%) with a similar pattern of underlying co-morbidities, most commonly hypertension (49.7%), followed by obesity (48.3%), DM (28.3%), and cardiovascular disease (27.8%). More than 70% of patients were older than 50 years. In another cross-sectional study, the same pattern of co-morbidities – hypertension (18.6%, $p < .001$), cardiovascular disease (14.4%, $p < .001$) and DM (11.9%, $p < .001$) – and male gender predominance (56%, $p < .001$) were observed in a population with an average age of 52 years [11]. Thus, it is noticeable that underlying co-morbidities and gender are similar among the different populations, but a mean age discrepancy exists between our cohort (average age of 40.6 years) and the other mentioned studies. This discrepancy might be due to the relative high percentage of young population in Israel where the median age in 2020 is 30.5 years, ten years younger than the populations in the USA and mainland China [20]. This is even more noticeable in particular settings, such as COVID-19 endemic cities, where population (especially, ultra-orthodox Jewish populations with a high number of children per family) is even younger with respect to the country.

Furthermore, more subjects positive for the COVID-19 infection were of lower SES status compared to controls (27.9% versus 12.7%), and more subjects negative for SARS-CoV-2 were of higher SES compared to positive subject (27.2% versus 36.4%). This is not surprising given the well-known association between low SES and increased risk for infections [21]. In the USA, minorities like African Americans and Hispanics have higher rates of mortality compared to the Caucasian population, largely due to SES disparities [22,23].

Concerning the alleged anti-viral activities of hydroxychloroquine [23] and its potential protective role against infections [24], the

existing scholarly literature reports contrasting findings even though to date no RCT has shown an unequivocal advantage in preventing or improving the major outcomes in COVID-19 patients [25,26]. Regarding the anti-inflammatory properties of colchicine, results from experimental models found that the NLRP3 inflammasome can be activated and triggered by different SARS-CoV-2 proteins and, subsequently, can take part in the development of the “severe adult respiratory distress syndrome” (ARDS), a complication of the COVID-19 infection [27–30]. As a major inhibitor of the NLRP3 inflammasome [31], colchicine could be utilized for the treatment of COVID-19. Currently, three clinical trials are ongoing [27,32,33]. However, in our investigation, we failed to detect a potential benefit of hydroxychloroquine and colchicine. Even though these drugs had not been administered for anti-viral treatment purposes, we were not able to identify the main reason of such an administration. On the other hand, we can assume that patients receiving these drugs suffer from inflammatory diseases such as RA and SLE in the case of hydroxychloroquine [34] and FMF and gout in the case of colchicine [35,36].

Despite the use of a large healthcare database, our study has several limitations that should be properly acknowledged: first, the relatively small number of patients who were documented to be a priori treated. Secondly, the basic methodology of the study, which is based on a computerized database, which might be incomplete. For instance, the duration and the reason of the treatment, as previously mentioned, are lacking. However, this study should be considered as a preliminary, pilot investigation, providing a first glance on the characteristics of patients with SARS-CoV-2 infection in Israel, showing that: 1) the median age of infected individuals is younger than their counterparts around the world, which warrants further research, and 2) that hydroxychloroquine and colchicine apparently provided no protection against the SARS-CoV-2 infection.

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References

- [1] World Health Organization. Pneumonia of unknown cause—C... - Google Scholar. 2020 https://scholar.google.com/scholar_lookup?hl=en&publication_year=2020&author=World+Health+Organization&title=Pneumonia+of+unknown+cause+%E2%80%94+China.#d=gs_cit&u=%2Fscholar%3Fq%3Dinfo%3AIPAb-NcXDLI%3Ascholar.google.com%2F%26output%3Dcite%26scirp%3D0%26hl%3Den Accessed 13 Apr 2020.
- [2] Appel S, Kaidar-Person O, Lawrence YR, Ben-Ayun M, Katzman T, Bar J, et al. The coronavirus pandemic in Israel: implications for radiation oncology departments. *IMAJ* 2020;22:211–3.
- [3] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020. <https://doi.org/10.1001/jama.2020.2648>. [Epub ahead of print].
- [4] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020. <https://doi.org/10.1056/NEJMoa2002032>.
- [5] Rodríguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Med Infect Dis* 2020:101623.
- [6] Sun J, He W-T, Wang L, Lai A, Ji X, Zhai X, et al. COVID-19: epidemiology, evolution, and cross-disciplinary perspectives. *Trends Mol Med* 2020;26(5):483–95.
- [7] Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. *Int J Infect Dis* 2020. <https://doi.org/10.1016/j.ijid.2020.03.017>.
- [8] Surveillances V. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China, 2020. *China CDC Weekly*. 2. 2020. p. 113–22.
- [9] Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol* 2020. <https://doi.org/10.1007/s00392-020-01626-9>.
- [10] Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. *JAMA* 2020;323:1335. <https://doi.org/10.1001/jama.2020.4344>. [Epub ahead of print].

- [11] Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell LF, Chernyak Y, et al. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City. medRxiv 2020.
- [12] COVID C, Team R. Severe outcomes among patients with coronavirus disease 2019 (COVID-19)—United States, February 12–march 16, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:343–6.
- [13] Kimball A, Hatfield KM, Arons M, James A, Taylor J, Spicer K, et al. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019—United States, February 12–march 28, 2020. 2020.
- [14] Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. *BMJ* 2020;368. <https://doi.org/10.1136/bmj.m1198>.
- [15] Lancet T. The gendered dimensions of COVID-19. *Lancet (London, England)* 2020;395:1168.
- [16] Shoenfeld Y. Corona (COVID-19) time musings: our involvement in COVID-19 pathogenesis, diagnosis, treatment and vaccine planning. *Autoimmun Rev* 2020;102538<https://doi.org/10.1016/j.autrev.2020.102538>. [Epub ahead of print].
- [17] Coronavirus_med_guidelines.pdf. 2020https://www.health.gov.il/Subjects/disease/corona/Documents/coronavirus_med_guidelines.pdf Accessed 14 Apr 2020.
- [18] Garg S. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—COVID-NET, 14 states, march 1–30, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69.
- [19] Country Comparison :: Median age — The World Factbook - Central Intelligence Agency. <https://www.cia.gov/library/publications/the-world-factbook/fields/343rank.html>; 2020 Accessed 19 Apr 2020.
- [20] Oestergaard LB, Schmiegelow MD, Bruun NE, Skov RL, Petersen A, Andersen PS, et al. The associations between socioeconomic status and risk of *Staphylococcus aureus* bacteremia and subsequent endocarditis – a Danish nationwide cohort study. *BMC Infect Dis* 2017;17:589.
- [21] Socioeconomic gradient in health and the COVID-19 outbreak. 2020<https://www.bmj.com/content/368/bmj.m755/rr-1> Accessed 19 Apr 2020.
- [22] Dyer O. Covid-19: black people and other minorities are hardest hit in US. *BMJ* 2020;369. <https://doi.org/10.1136/bmj.m1483>.
- [23] Savarino A, Trani LD, Donatelli I, Cauda R, Cassone A. New insights into the antiviral effects of chloroquine. *Lancet Infect Dis* 2006;6:67–9.
- [24] Ruiz-Irastorza G, Olivares N, Ruiz-Arruza I, Martinez-Berriotxo A, Egurbide M-V, Aguirre C. Predictors of major infections in systemic lupus erythematosus. *Arthritis Res Ther* 2009;11:R109.
- [25] Rubin EJ, Baden LR. Morrissey SAudio Interview: Loosening Covid-19 Restrictions. *N Engl J Med* 2020;382:e67.
- [26] Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA* 2020. <https://doi.org/10.1001/jama.2020.6019>. [Epub ahead of print].
- [27] Deftereos SG, Siasos G, Giannopoulos G, Vrachatis DA, Angelidis C, Giotaki SG, et al. The GREEK study in the effects of colchicine in COVID-19 complications prevention (GRECCO-19 study): rationale and study design. *Hellenic J Cardiol* 2020. <https://doi.org/10.1016/j.hjc.2020.03.002>.
- [28] Kanduc D, Shoenfeld Y. On the molecular determinants the SARS-CoV-2 attack. *Clin Immunol (Orlando, Fla)* 2020;18:215. 108426.
- [29] Kerpel A, Nissan N, Klug M, Amit S, Konen E, Marom EM. Imaging findings in four COVID-19 patients. *IMAJ* 2020;22:214–5.
- [30] Infantino M, Damiani A, Gobbi FL, Grossi V, Lari B, Macchia D, et al. Serological assays for SARS-CoV-2 infectious disease: benefits, limitations and perspectives. *IMAJ* 2020;22:203–10.
- [31] Leung YY, Hui LLY, Kraus VB. Colchicine — update on mechanisms of action and therapeutic uses. *Semin Arthritis Rheum* 2015;45:341–50.
- [32] Colchicine Counteracting Inflammation in COVID-19 Pneumonia - Full Text View. *ClinicalTrials.gov*; 2020<https://clinicaltrials.gov/ct2/show/NCT04322565> Accessed 21 Apr 2020.
- [33] Colchicine coronavirus SARS-CoV2 trial (COLCORONA) - full text view - *ClinicalTrials.gov*. <https://clinicaltrials.gov/ct2/show/NCT04322682>. 2020 Accessed 14 Apr 2020.
- [34] Tang C, Godfrey T, Stawell R, Nikpour M. Hydroxychloroquine in lupus: emerging evidence supporting multiple beneficial effects. *Intern Med J* 2012;42:968–78.
- [35] Pascart T, Richette P. Colchicine in gout: an update. *Curr Pharm Des* 2018;24:684–9.
- [36] Grossman C, Farberov I, Feld O, Livneh A, Ben-Zvi I. Efficacy and safety of long-term treatment with intravenous colchicine for familial Mediterranean fever (FMF) refractory to oral colchicine. *Rheumatol Int* 2019;39:517–23.