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RESEARCH ARTICLE

A Randomized Controlled Trial of Hydroxychloroquine as Prophylaxis for COVID-19 among Health Care Providers

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Abstract:

Background:

Although there is a growing consensus that hydroxychloroquine may not be effective in the treatment of COVID-19 patients, there is still little high-quality evidence about the prophylactic effects of this medication. In this study, we aimed to evaluate the efficiency of hydroxychloroquine in preventing COVID-19 infection among healthcare workers.

Methods:

In this clinical trial, 90 healthcare providers from two referral hospitals of COVID-19 were divided into the hydroxychloroquine group (400 mg/week for eight weeks) and the routine-care group. Serum CRP levels and the frequency of T-helper (CD4+ cells) and T-cytotoxic (CD8+ cells) were assessed at the beginning and end of the study. The groups were compared in terms of White Blood cells (WBCs), polymorph nuclear cells (PMNs), lymphocytes (LYM), hemoglobin (Hb), and platelets (Plt.).

Results:

The results revealed no significant differences between the two groups in terms of WBC, PMN, LYM, Hb, Plt., CD4, and CD8. The mean difference of the CD4:CD8 ratio showed a significantly higher decrease ($P=0.05$) in hydroxychloroquine group than in the control group (0.18 vs. 0.02). The incidence of COVID-19 was 15% (95%CI: 12-18%) in the control group and 10% (95%CI: 8-12%) in the intervention group; however, no significant difference was observed between the two groups in this regard ($P=0.45$).

Conclusion:

Our study findings boost an increasing level of evidence that hydroxychloroquine is not an effective prophylactic medication against COVID-19 and might even exacerbate the profile of pandemic containment efforts by adding more pain to patients' life and healthcare services.

Keywords: Hydroxychloroquine, Prophylaxis, COVID-19, Healthcare providers, Clinical trial, Participants.

Article History

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1. INTRODUCTION

A novel coronavirus (SARS-CoV-2), which leads to a severe acute respiratory syndrome in severe cases, has turned into a public health emergency [1]. However, there is no post-exposure prophylaxis or definitive treatment yet for the disease, which poses a huge challenge in taming the pandemic.

Nonetheless, there is a galvanized attempt worldwide to at least find post-exposure prophylaxis (PEP) for high-risk people and front-line health workers as they are at greater risk of infection by COVID-19 [2]. Re-purposing the available medication has been one of the main sources of such attempts. Among the current medications, hydroxychloroquine has the potential to be used as PEP since it is shown to be effective in blocking SARS-CoV-2 or MERS-CoV *in-vitro* [3, 4].

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However, some studies demonstrate no significant association between hydroxychloroquine use and prevention, improvement, and recovery from COVID-19 [5 - 9]. For instance, in a randomized double-blinded clinical trial on people who had close contact with confirmed COVID-19 patients either as a family member or a hospital staff, it was shown that hydroxychloroquine was not significantly different from placebo in terms of preventing the disease after 14 days [6]. This finding has been repeated in other three observational studies as well [10, 11]. More importantly, the most comprehensive clinical trial, conducted by World Health Organization (WHO) called Solidarity Therapeutics Trial, has recently shown that none of the repurposed medications, including hydroxychloroquine, were effective in the treatment of hospitalized COVID-19 patients (both in terms of hospital course of the disease and its mortality). However, this trial called for more studies to investigate the preventive effects of these medications on a larger scale [9]. In contrast, a couple of studies have shown that hydroxychloroquine alone or in combination with azithromycin could reduce the mortality rate of patients with COVID-19 [5, 12]. Therefore, although there is a growing consensus that hydroxychloroquine may not be effective in treating COVID-19 patients [7, 8], there is still little high-quality evidence about the prophylactic effects of this medication [7].

In this randomized clinical trial, as a result, we aimed to evaluate the efficiency of hydroxychloroquine in preventing COVID-19 infection among healthcare workers in two hospitals in Iran.

2. MATERIALS AND METHODS

2.1. Study Design

The present study is an open-labeled randomized controlled clinical trial in which 90 healthcare providers from two referral hospitals of COVID-19 were randomly divided into two groups; one group received hydroxychloroquine, and the other group received routine care. This study was registered in the Iranian Registry of Clinical Trials in May 2020 (IRCT code: IRCT20151222025660N2). Also, this study was approved by the Ethical Committee of Arak University of Medical Sciences in March 2020 (Ethic Code: IR.ARAKMU.REC.1398.345). All the experimental protocols were approved by the vice-chancellor for Research of the Arak University of Medical Sciences.

At the beginning of the study, the study conditions were fully explained to the participants, the necessary explanation about the medications was given, and the subjects were also informed that they were randomly assigned to one of these two groups. Furthermore, they were assured that their information would be kept confidential, and they could decide to leave the study at any stage without providing any explanation for their decision. No additional costs were also imposed on participants. Researchers felt obliged to observe all the ethical clauses required in human research.

2.2. Participants

Participants in this study included physicians, nurses,

paramedics, and other healthcare providers working in COVID-19 referral hospitals in Arak. The inclusion criteria were as follows: provision of informed consent to participate in the study, working in medical centers in Arak, insensitivity to hydroxychloroquine, and lack of G6PD deficiency, porphyria, breastfeeding, pregnancy, diabetes, and any renal, liver, and skin disorders. Participants were also excluded from the study if they did not wish to continue the study or were allergic to hydroxychloroquine. Patients' recruitment lasted from April 20, 2020, to May 30, 2020. The study lasted about 6 months.

2.3. Intervention

Chloroquine and hydroxychloroquine are originally used to prevent and treat malaria. Due to the fact that the ocular complications of hydroxychloroquine are less than chloroquine, the former is commonly used and is even prescribed for the treatment of rheumatic diseases. In this study, participants in the intervention group received 400 mg/week of hydroxychloroquine for eight weeks, and participants in the control group received routine care for COVID-19.

2.4. Measurements

The COVID-19 occurrence was compared between the two groups. Diagnosis of the COVID-19 was syndromic in the sense that if there were clinical symptoms indicative of COVID-19, *i.e.*, high fever and dry cough, a CT scan was requested for the participants. Following a national guideline for the disease, COVID19-PCR was requested to confirm the preliminary diagnosis if the scan results came positive.

Serum CRP levels by ELISA method (according to manufacture of kit) and the frequency of T-helper (CD4+ cells) and T-cytotoxic (CD8+ cells) by flow cytometry were assessed at the beginning and end of the study for all participants. The two groups were also compared in terms of White Blood Cells (WBCs), polymorph nuclear cells (PMNs), lymphocytes (LYM), hemoglobin (Hb), and platelets (Plt.).

2.5. Randomization and Blinding

This study was conducted in two referral hospitals for COVID-19. For logistical reasons, we decided to randomly allocate the staff of one hospital to the intervention group and the staff of another hospital to the control group. This allocation method was more appropriate for us both in terms of study implementation and also prevention of information leakage between the two groups. There was no blinding in the design of this study, and the study was open-labeled. However, the baseline characteristics were compared between the two groups.

2.6. Statistical Analysis and Sample Size

Mean and standard deviations were used to describe quantitative data. Frequency and percentage were used for qualitative data. Independent sample t-test, log-likelihood ratio chi-square, and binary logistic regression were primarily used to analyze the data. We aimed to assess the effect of hydroxychloroquine on the incidence of COVID-19 by a log-binomial regression model, but a convergence problem arose.

Therefore, a modified Poisson regression model was used to estimate the risk ratios (RRs) and its 95% confidence intervals (CIs) [13]. All the analyses were performed using Stata software version 14 at a significance level of 0.05. We expected that a total of 90 cases were needed (45 cases in each group) to achieve a 25% difference in COVID-19 occurrence between the two groups with a power of 80%. A P-value <0.05 was considered as a level of significance.

3. RESULTS

We primarily planned to assign 45 healthcare providers to each group. However, 1 case in the control group and 13 cases in the intervention group were excluded from the study (due to different reasons, such as non-appropriate compliance, reluctance to continue the participation, worry about side effects of hydroxychloroquine, etc). Therefore, 44 cases in the control group and 32 cases in the intervention group were finally included in the analyses.

The baseline characteristics are presented in Table 1. As the table illustrates, there was no difference between the two study groups in terms of gender composition, mean of WBCs, PMNs, LYM, Hb, Plt, CD4, CD8, and the ratio of CD4 to CD8. The mean ages in the intervention and control groups were 36.8 (S.D.±6.7) and 33.3 (S.D.±7.9), respectively, which indicates a significant difference ($p = 0.04$) between the two groups. Accordingly, we conducted an age-adjusted analysis to compare the targeted outcomes between the two groups. Also,

there was no significant difference among the two groups according to C-reaction protein (CRP) at the baseline ($p=0.33$) and after intervention ($p=0.29$).

As shown in Table 2, two methods of end-of-study and before-after-comparison were used to compare the variables between the two groups. In the first method, the mean of the variables was compared 8 weeks after the intervention using an independent sample t-test. The results of this comparison showed that the two groups did not differ significantly in terms of WBCs ($p=0.51$), PMNs ($p=0.95$), LYM ($p=0.53$), Hb ($p=0.37$), Plt. ($p=0.69$), CD4 ($p=0.23$), CD8 ($p=0.69$), and the ratio of CD4 to CD8 ($p=0.33$). In the second method, to adjust the values of the variables in the baseline, the amount of changes in each variable (values after the intervention minus the baseline values) was calculated in the first place. Then, to control the effect of age, the calculated changes were compared between the two groups using a multiple linear regression model. The results of these analyses revealed that there were no significant differences between the two groups in terms of WBCs ($p=0.65$), PMNs ($p=0.97$), LYM ($p=0.98$), Hb ($p=0.97$), Plt. ($p=0.36$) and CD8 ($p=0.92$). The mean difference of CD4 to CD8 showed a higher decrease in hydroxychloroquine group than the control group (0.18 vs. 0.02), and it was significant ($P=0.05$). To be precise, the mean changes in CD4 were significantly different between the two groups, showing a significant increase in the control group (4.2), much higher than the intervention group (0.32).

Table 1. Baseline comparison of the intervention and control groups.

Variables	Hydroxychloroquine Group (n=32)	Control Group (n=44)	P-value
Gender, Female, n (%)	24 (75.0%)	34 (77.3%)	0.82
Age, mean (S.D.)	36.8 (6.7)	33.3 (7.9)	0.04
WBC, mean (S.D.)	6.9 (1.4)	6.8 (1.6)	0.73
PMN, mean (S.D.)	56.2 (8.2)	55.6 (8.2)	0.74
LYM, mean (S.D.)	34.9 (6.4)	35.9 (7.7)	0.53
Hb, mean (S.D.)	13.4 (1.4)	13.7 (1.8)	0.39
Plt., mean (S.D.)	234.4 (53.2)	235.3 (59.3)	0.94
CD4, mean (S.D.)	36.5 (7.9)	34.6 (7.0)	0.26
CD8, mean (S.D.)	23.2 (5.8)	23.9 (7.4)	0.66
Ratio of CD4:CD8, mean (S.D.)	1.62 (0.33)	1.56 (0.47)	0.55

Table 2. The comparison of interested outcomes between intervention and control groups.

Variables	Mean at the End of Study (8 th Weeks)			Mean Difference (After-Before)		
	Hydroxychloroquine Group (n=32)	Control Group (n=44)	P-value	Hydroxychloroquine Group (n=32)	Control Group (n=44)	P-value*
WBC, mean (S.D.)	7.25 (1.6)	7.00 (1.6)	0.51	0.34 (1.4)	0.22 (1.4)	0.65
PMN, mean (S.D.)	56.9 (8.4)	56.8 (6.4)	0.95	0.65 (8.2)	1.2 (6.3)	0.97
LYM, mean (S.D.)	33.8 (8.1)	34.9 (6.8)	0.53	-1.0 (7.2)	-1.0 (5.2)	0.98
Hb, mean (S.D.)	13.1 (0.92)	13.4 (1.5)	0.37	-0.31 (1.15)	-0.37 (1.7)	0.97
Plt., mean (S.D.)	245.1 (58.7)	239.4 (63.7)	0.69	10.6 (61.5)	4.0 (48.3)	0.36
CD4, mean (S.D.)	36.9 (8.4)	38.8 (5.6)	0.23	0.32 (8.7)	4.2 (8.5)	0.04
CD8, mean (S.D.)	26.5 (5.2)	27.0 (6.3)	0.69	3.2 (7.4)	3.1 (5.9)	0.92
Ratio CD4:CD8,	1.4 (0.4)	1.5 (0.5)	0.33	-0.18 (0.41)	-.02 (0.32)	0.05

*Adjusted for age.

Also, in the intervention group, the mean levels of CD4, CD8, and the ratio of CD4 to CD8 were compared before and after the intervention. The results showed that the level of CD4 did not change significantly ($P=0.835$); however, a significant increase in the mean CD8 ($P=0.018$) and also a significant decrease in the ratio of CD4 to CD8 ($P=0.016$) were observed after hydroxychloroquine intake.

Finally, the two groups were compared in terms of COVID-19 incidence. The incidence of COVID-19 was 15% (95% CI: 12-18%) in the control group and 10% (95% CI: 8-12%) in the intervention group, but there was no statistically significant difference between the two groups in this regard ($P=0.45$). To be precise, four COVID-19 cases (9.1%) were observed in the control group and three cases (9.4%) in the hydroxychloroquine group, and there was no statistically significant difference between the two groups (RR; 0.99, 95% CI: 0.86-1.15, $P=0.966$), even after age adjustment (RR; 0.96, 95% CI: 0.83-1.11, $P=0.629$).

4. DISCUSSION

In an open-labeled RCT, the authors of the present study aimed to investigate the prophylactic effects of hydroxychloroquine in a hospital setting.

According to our findings, there was no significant difference between the control and intervention groups in terms of COVID-19 incidence, implying that hydroxychloroquine did not act as a prophylactic agent. However, there were some serologic differences between the two groups. Namely, the mean of CD4 increased significantly after the intervention in the control group (compared to its baseline mean) but almost stayed the same in the test group. This finding can be alarming as it shows that hydroxychloroquine does not prevent COVID-19 incidence, but at a cellular level, it might undermine the immune system's capabilities by slowing down the growth of CD4 cells.

Our findings are in line with the findings of an RCT-based (*i.e.*, Boulware *et al.*) study demonstrating that hydroxychloroquine is not an effective prophylactic agent against COVID-19 [6]. This is also in line with two other available observational studies, *i.e.*, a retrospective study conducted by Gendelman *et al.* [10] on the general public and a prospective study by König *et al.* [11] on patients with Systemic Lupus Erythematosus stating that hydroxychloroquine consumption did not prevent from infection. Interestingly, our findings are a timely response to WHO's Solidarity Therapeutics Trial; however, other systematic reviews call for more preventive-oriented studies on repurposed medications.

Our finding regarding the negative effects of hydroxychloroquine on CD4 level growth is also in line with similar findings reported for its use for other diseases (*e.g.*, Rheumatic disease and HIV) [14, 15]. Research revealed that the CD4:CD4 ratio was not different among COVID-19 patients and healthy individuals; however, CD8 expression was significantly higher in COVID-19 patients than in normal individuals [16]. Moreover, it was also observed that patients with COVID-19 have prominent cytokine profiles of Th1 and Th17 [17]. Interestingly, there is also evidence that the COVID-19 virus itself reduces the CD4 and CD8 counts in

patients [18, 19]. This may have two different possibilities: first, the immune system of people who receive hydroxychloroquine will be quite compromised and might be a reason behind its ineffectiveness to act as a therapeutic or prophylactic medication; second, decreasing CD4 cells and increasing CD8 cells after hydroxychloroquine may provide some protection against the severe form of COVID-19, *i.e.*, lowering cells incorporating in a cytokine storm (*i.e.*, CD4 cells) and augmenting cellular immunity (*i.e.*, CD8 cells). Considering these facts together may add more power to increasing precautionary messages regarding short- and long-term complications of hydroxychloroquine use [20]. For instance, one of the most comprehensive and updated reviews on the therapeutic and prophylactic effects of hydroxychloroquine has concluded that the use of this medication should only be limited to RCTs where monitoring of its complications is possible [7].

Since there are limited studies on COVID-19, the design and implementation of this study as a clinical trial are strengths of this study. Moreover, one of the limitations of this study is the limited sample size as this study was conducted at the beginning of the epidemic in a single center; therefore, similar studies should be designed with a larger sample size in other populations. Another limitation of this study is that 15% of the participants were excluded from the study, which was mainly in the intervention group, which could be due to fear of HCQ side effects.

CONCLUSION

Overall, our study findings boost an increasing level of evidence that hydroxychloroquine is not an effective prophylactic medication against COVID-19 and might even exacerbate the profile of pandemic containment efforts by adding more pain to patients' life and healthcare services. Moreover, further studies are recommended to reach a better conclusion.

LIST OF ABBREVIATIONS

WBCs	=	White Blood Cells
PMNs	=	Polymorph Nuclear Cells
LYM	=	Lymphocytes
Hb	=	Hemoglobin
Plt	=	Platelets
RCT	=	Randomized Controlled Trial
RR	=	Risk Ratio
CI	=	Confidence Interval
PEP	=	Post-Exposure Prophylaxis

AUTHORS' CONTRIBUTIONS

RP, GM, AAH, and NZ contributed to the conception and design of the study. Data collection, statistical analysis, and interpretation of data were performed by RP, GM, AAH, NZ, SZR, SN, and MMH. RP, GM, AAH, SZR, NZ, SN, and MMH participated in manuscript preparation, supervision, and critical revision of the paper and provided administrative support. All authors read and approved the final manuscript.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This study was registered in the Iranian Registry of Clinical Trials in May 2020 (IRCT code: IRCT20151222025660N2). Also, this study was approved by the Ethical Committee of Arak University of Medical Sciences in March 2020 (Ethic Code: IR.ARAKMU.REC.1398.345).

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All human research procedures were followed 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

Written informed consent was obtained from all the participants.

AVAILABILITY OF DATA AND MATERIALS

The data supporting findings of this study is available from the corresponding author [A.A.-H], upon reasonable request.

STANDARDS OF REPORTING

CONSORT guidelines and methodologies were followed for this study.

FUNDING

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CONFLICT OF INTEREST

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

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REFERENCES

- [1] World Health Organization. Weekly Operational update on COVID-19 - 23. 2020.
- [2] Nguyen LH, Drew DA, Graham MS, *et al.* Risk of COVID-19 among front-line health-care workers and the general community: A prospective cohort study. *Lancet Public Health* 2020; 5(9): e475-83. [http://dx.doi.org/10.1016/S2468-2667(20)30164-X] [PMID: 32745512]
- [3] Picot S, Marty A, Bienvenu A-L, *et al.* Coalition: Advocacy for prospective clinical trials to test the post-exposure potential of hydroxychloroquine against COVID-19. *One Health* 2020; 9:100131 [http://dx.doi.org/10.1016/j.onehlt.2020.100131] [PMID: 32292817]
- [4] Tahiri Joutei Hassani R, Bennis A. Hydroxychloroquine as antiviral prophylaxis for exposed caregivers to COVID-19: An urgent appraisal is needed. *J Infect Public Health* 2020; 13(6): 865-7. [http://dx.doi.org/10.1016/j.jiph.2020.05.005] [PMID: 32451259]
- [5] Geleris J, Sun Y, Platt 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]
- [6] Boulware DR, Pullen MF, Bangdiwala AS, *et al.* A randomized trial of hydroxychloroquine as postexposure prophylaxis for COVID-19. *N Engl J Med* 2020; 383(6): 517-25. [http://dx.doi.org/10.1056/NEJMoa2016638] [PMID: 32492293]
- [7] Cortegiani A, Ippolito M, Ingoglia G, Iozzo P, Giaratano A, Einav S. Update I. A systematic review on the efficacy and safety of chloroquine/hydroxychloroquine for COVID-19. *J Crit Care* 2020; 59: 176-90. [http://dx.doi.org/10.1016/j.jccr.2020.06.019] [PMID: 32683212]
- [8] Siemieniuk RA, Bartoszko JJ, Ge L, *et al.* Drug treatments for covid-19: Living systematic review and network meta-analysis. *BMJ* 2020; 370: m2980. [http://dx.doi.org/10.1136/bmj.m2980] [PMID: 32732190]
- [9] Pan H, Peto R, Abdool Karim Q, *et al.* Repurposed antiviral drugs for COVID-19; Interim WHO SOLIDARITY trial results medRxiv 2020.
- [10] Gendelman O, Amital H, Bragazzi NL, Watad A, Chodick G. Continuous hydroxychloroquine or colchicine therapy does not prevent infection with SARS-CoV-2: Insights from a large healthcare database analysis. *Autoimmun Rev* 2020; 19(7): 102566. [http://dx.doi.org/10.1016/j.autrev.2020.102566] [PMID: 32380315]
- [11] Arnold SLM, Buckner F. Hydroxychloroquine for treatment of SARS-CoV-2 infection? Improving our confidence in a model-based approach to dose selection. *Clin Transl Sci* 2020; 13(4): 642-5. [http://dx.doi.org/10.1111/cts.12797] [PMID: 32268005]
- [12] Castelnovo AD, Costanzo S, Antinori A, *et al.* Use of hydroxychloroquine in hospitalised COVID-19 patients is associated with reduced mortality: Findings from the observational multicentre Italian CORIST study. *Eur J Intern Med* 2020; 82: 38-47. [http://dx.doi.org/10.1016/j.ejim.2020.08.019] [PMID: 32859477]
- [13] Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; 159(7): 702-6. [http://dx.doi.org/10.1093/aje/kwh090] [PMID: 15033648]
- [14] Paton NI, Goodall RL, Dunn DT, *et al.* Effects of hydroxychloroquine on immune activation and disease progression among HIV-infected patients not receiving antiretroviral therapy: A randomized controlled trial. *JAMA* 2012; 308(4): 353-61. [http://dx.doi.org/10.1001/jama.2012.6936] [PMID: 22820788]
- [15] Schmidt RLJ, Jutz S, Goldhahn K, *et al.* Chloroquine inhibits human CD4⁺ T-cell activation by AP-1 signaling modulation. *Sci Rep* 2017; 7(1): 42191. [http://dx.doi.org/10.1038/srep42191] [PMID: 28169350]
- [16] Ganji A, Farahani I, Khansarinejad B, Ghazavi A, Mosayebi G. Increased expression of CD8 marker on T-cells in COVID-19 patients. *Blood Cells Mol Dis* 2020; 83:102437 [http://dx.doi.org/10.1016/j.bcmd.2020.102437] [PMID: 32325421]
- [17] Ghazavi A, Ganji A, Keshavarzian N, Rabiemajid S, Mosayebi G. Cytokine profile and disease severity in patients with COVID-19. *Cytokine* 2021; 137:155323 [http://dx.doi.org/10.1016/j.cyto.2020.155323] [PMID: 33045526]
- [18] Chen G, Wu D, Guo W, *et al.* Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020; 130(5): 2620-9. [http://dx.doi.org/10.1172/JCI137244] [PMID: 32217835]
- [19] Diao B, Wang C, Tan Y, *et al.* Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). *Front Immunol* 2020; 11: 827. [http://dx.doi.org/10.3389/fimmu.2020.00827] [PMID: 32425950]
- [20] Nagaraja BS, Ramesh KN, Dhar D, *et al.* HyPE study: hydroxychloroquine prophylaxis-related adverse events' analysis among healthcare workers during COVID-19 pandemic: A rising public health concern. *J Public Health (Oxf)* 2020; 42(3): 493-503. [http://dx.doi.org/10.1093/pubmed/fdaa074] [PMID: 32490532]