ORIGINAL ARTICLE

Hydroxychloroquine for COVID-19: A Single Center, Retrospective Cohort Study

Wen Chung Ho[1], Wei Xin Yong[2,3], Khai Shin Tan[4], Woh Yon Mak[5], Mandeep Kaur Gill[5], Agnes Hui Ching Lok[5], Shazwani Zulkifli[5], Salmah Idris[6], Khairil Erwan Khalid[4], Chee Loon Leong[4], Kang Nien How[2,3]

[1] Department of Medicine, Hospital Serdang, Kajang, Selangor, Malaysia.
[2] Dermatology Unit, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Selangor, Malaysia
[3] Dermatology Unit, Hospital Pengajar Putra Malaysia, University Putra Malaysia, Selangor, Malaysia.
[4] Infectious Disease Unit, Department of Medicine, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia.
[5] Department of Pharmacy, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia.
[6] Department of Pathology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia.

ABSTRACT

Introduction: The outbreak of coronavirus disease (COVID-19) in December 2019 called for a rapid solution, leading to repurposing of existing drugs. Due to its immunomodulatory effect and antiviral properties, hydroxychloroquine (HCQ) has been used in early 2020 for treatment of COVID-19 patients. This study was conducted to evaluate the treatment outcome of HCQ monotherapy in Malaysia. **Methods:** A retrospective cohort study was conducted in COVID-19 ward in Hospital Kuala Lumpur (HKL), from March to April 2020. A total of 446 COVID-19 patients were recruited, only 325 patients were finally included for analysis. Statistical analysis was done using SPSS, with a significant value set at $p<0.05$. **Results:** The mean age of the patients were 38.5 ±15.5. They were majority male, (n=210, 64.6%) Malaysian (n=239, 73.5%) and Malay ethnicity (n=204, 62.8%). Ninety-one (28%) patients received HCQ monotherapy. HCQ monotherapy was associated with worse outcome (OR: 10.29, 95% CI 1.17-90.80). There was a significant difference in mean length of stay between those with and without HCQ treatment ($t323=5.868$, $p<0.001$, 95% CI, 2.56-5.31). The average length of stay for HCQ treated group was 3.84 days longer than those without treatment. 6.6% of the patient receiving HCQ monotherapy encountered adverse drug effects. **Conclusion:** Similar to study reported worldwide, our study demonstrated that HCQ did not improve length of stay and the outcome of COVID-19 patients.
Malaysian Journal of Medicine and Health Sciences (2023) 19(2):8-13. doi:10.47836/mjmhs19.2.3

Keywords: Hydroxychloroquine, COVID-19, Coronavirus, Antiviral, Efficacy

Corresponding Author:
Kang Nien How, MRCP
Email: hkangnien@upm.edu.my
Tel: +603-97695601

INTRODUCTION

The world is still devastated by Coronavirus Disease 2019 (COVID-19) since it first reported in December 2019. Until February 2022, World health organization (WHO) has reported up to total of 400 million confirm cases with 5 million deaths worldwide (1). Novel oral antivirals such as Molnupiravir and Paxlovid are found to be effective in reducing the mortality and hospitalization rates in patients with COVID-19, but are not readily available in most of the countries (2). In the beginning of this pandemic, few drugs with antiviral property such as Chloroquine (CQ), Hydroxychloroquine (HCQ), Remdesivir and Lopinavir / Ritonavir, were being repurposed and used as off-label medications to fight COVID-19 (3). CQ and its safer hydroxyl analogue

HCQ have been widely used as an antimalarial (4). Moreover, HCQ is used as an immunomodulator and anti-thrombotic in various autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and antiphospholipid syndrome (5). The studies of CQ's antiviral properties are dated back to the late 1960s (6). CQ and HCQ antiviral properties were supported by in vitro study. Liu et al and Wang et al demonstrated that CQ and HCQ are able to inhibit entry, duplication and release of SARS-CoV-2 in infected kidney epithelial cells of African green monkey by glycosylation of ACE2 receptors and increase endosomal pH (7-9). Based on pharmacokinetic models for treatment of COVID 19, Yao et al suggested the optimal dosage of HCQ will be 400mg twice daily on day one and 200mg twice daily for another 4 days (8). Positive results from in vitro study have led to off-label uses as well as clinical trials of CQ and HCQ worldwide to combat COVID-19. The positive results from France and China have motivated large scale multicentred and international clinical trial (10-12). Nonetheless, more recent evidence has found

no benefit in using HCQ in COVID-19 and thus FDA has revoked the use of HCQ and CQ (13-16). When the disease first struck Malaysia in early 2020, HCQ was used as an off-label treatment against COVID-19 in many centres in Malaysia, including Hospital Kuala Lumpur. In order to determine the outcome of HCQ treated COVID-19 patients among our own population, we had conducted this retrospective comparative cohort study.

MATERIALS AND METHODS

Study design
This was a single-centre retrospective cohort study done in Hospital Kuala Lumpur. This study had obtained approval from Medical Research & Ethics Committee, Ministry of Health in May 15, 2020. (KKM/NIHSEC/ P20-1099 (6)).

Study population
All patients aged above 18 years admitted to COVID-19 wards in Hospital Kuala Lumpur (HKL) with or without HCQ monotherapy from 1st March 2020 to 30th April 2020 were included in this study. Children and those who were on treatment other than HCQ monotherapy were excluded from analysis.

Data collection
Patients' hard copy health medical records were retrieved from the hospital record office and data collection was conducted using a structured data collection form. Data collected include demographic parameters, clinical symptoms and severity of COVID-19 according to category (Category 1, asymptomatic patient; Category 2, symptomatic patient but absent of pneumonia; Category 3, symptomatic patient with pneumonia; Category 4, symptomatic patient with pneumonia and requiring oxygen supplementation; Category 5, critically ill with multiorgan involvement.) (17). HCQ was indicated patient with category 2 plus warning signs of further deterioration, category 3, category 4 and category 5 disease. (Supplementary data for full information) Day of illness where HCQ was initiated and total duration of treatment were collected as well.

Patients who received HCQ monotherapy (Dose: 800mg/day on day one, follow by 400mg/day for 4 days) were compared to patients who did not receive HCQ monotherapy.

The primary outcome of this study was difference in clinic response (improved or worsened) between the two cohorts, with or without HCQ monotherapy. Improved clinical response was defined as discharged well from hospital and worsened clinical response was defined as increased requirement in oxygen supplementation, requiring non-invasive ventilation, invasive ventilation, or ICU admission and death. Secondary outcomes include length of hospital stay and side effects of HCQ.

Statistical analysis
Qualitative variables were expressed in frequency and percentage while quantitative variables were expressed in mean with standard deviation. Statistical evaluation was utilized to determine if there is association in the distribution of variables (Chi-Square test) between HCQ and non HCQ cohorts, Chi-Square test was used for categorical variables and Student T test was used for continuous variables. All analyses were conducted using IBM SPSS Statistics version 26 where p value of <0.05 was considered statistically significant.

RESULTS

A total of 446 COVID-19 patients were admitted to HKL from March 1 2020 to April 30 2020. 84 patients were excluded as they were on treatment other than HCQ monotherapy. One patient was excluded due to incomplete information. 27 patients were excluded due to age less than 18-year-old and 9 patients were excluded due to duplicate record. Finally, 325 patients were included for analysis. These patients were separated into two groups namely HCQ (n=91) and non-HCQ (n=234). (Figure 1).
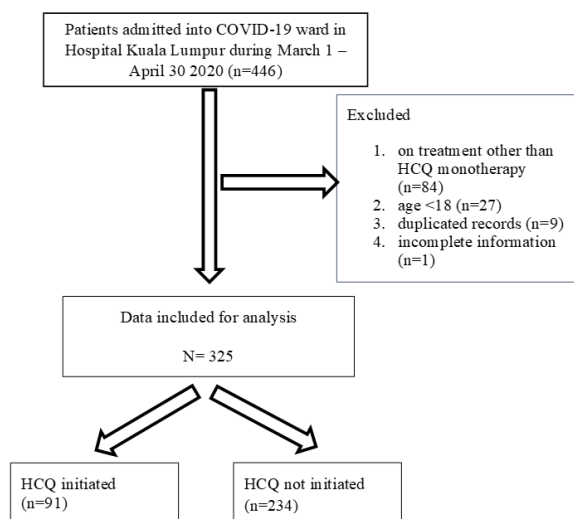
Figure 1:Flow Diagram of All Cases Included

Demographic
64% of the patients were male with mean age of 39.5 ± 15.6 years. Most of the patients were Malaysian (73.5%, n=239). In terms of ethnicity, Malays were the majority (62.8%, n=204), followed by Chinese (9.5%, n=31), Indian (4.3%, n=14) and others (23.4%, n=76). Most of the patients had no comorbidity (72%, n=234). Hypertension was the most common comorbid (17.8%, n=58) followed by diabetes mellitus (10.5%, n=34), dyslipidaemia (4.6%, n=15), ischemic heart disease (4%, n=13), asthma (2.2%, n=7) and stroke (0.3%, n=1). More than half of the patients presented with Category 2 (51.7%, n=168) followed by Category 1 (42.2%, n=137), Category 3 (4%, n=13), Category 4 (1.5%, n=5) and

Category 5 (0.6%, n=2). Majority of the patients were symptomatic (65.2%, n=212). Cough, fever, sore throat, and runny nose were the most common manifesting symptoms (40.6%, n=130; 40%, n=132; 17.8%, n=58; 12.3%, n=40; respectively). Gastrointestinal symptoms such as diarrhoea, vomiting and nausea were recorded in 7.1% (n=23), 1.5% (n=5) and 0.9% (n=3) of the patients.

HCQ initiation

Among the HCQ cohort, HCQ was initiated within a mean 8.05 ± 6.42 days of illness. The mean duration of treatment was 6.4 ± 2.75 days. There was no statistical difference in terms of gender, age, nationality, and comorbidities between both cohorts. However, severity of the illness on presentation and presence of symptoms were found to have significant association with p value of <0.001 and 0.006 respectively (Table I).

Primary Outcome

95.6% (n=87) of those who received HCQ had recovered while 99.6% (n=233) of those not receiving HCQ had recovered. This difference was significant (p = 0.009,
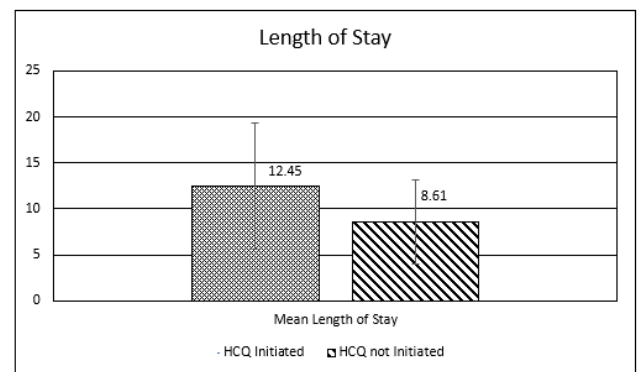
OR: 10.29; 95% CI 1.17-90.80). More patients in the HCQ arm were reported to have deteriorated (n= 4), while only one from the non-HCQ cohort experienced the same. Among patients who deteriorated, two required invasive ventilation, one required treatment escalation, one transferred to intensive care unit, and one transferred to another facility for advance care but we were unable to trace further information (Table II).

Table II: Outcomes

	HCQ		p Value	odd ratio (95% CI)
	Initiated (n=91)	Not initiated (n=234)		
Outcome (%)				
Recovered	87 (95.6)	233 (99.6)	0.009	10.29 (1.17-90.80)
Worsened	4 (4.4)	1 (0.4)		

Secondary Outcome

A numerical longer mean length of stay was observed in the HCQ cohort, (12.45 ± 6.872 days vs 8.61 ± 4.553 days, ($t323=5.868$, $p<0.001$, 95% CI 2.56-5.31) (Figure 2). Among those who received HCQ, 6.6% (n=6) experienced adverse effects. Transaminitis (3.3%, n=3) was the most common adverse effect followed by combined acute liver and kidney injury (2.2%, n=2). Only one (1.1%) patient reported to have gastrointestinal side effect.

Table I: Demographic characteristics

	HCQ		Total	P Value
	Initiated (n=91)	Not initiated (n=234)		
Gender				
Male	54 (59.3)	156 (66.7)	210 (64.6)	0.215
Female	37 (40.7)	78 (33.3)	115 (35.4)	
Age, Mean (SD)	42.19 (16.946)	38.46 (14.908)	38.5 (15.5)	0.111**
Nationality				
Malaysian	630 (69.2)	176 (75.2)	239 (73.5)	0.272
Non-Malaysian	28 (30.8)	58 (24.8)	86 (26.5)	
Ethnicity				
Malay	49 (53.8)	155 (66.2)	204 (62.8)	
Chinese	15 (16.5)	16 (6.8)	31 (9.5)	0.042
Indian	4 (4.4)	10 (4.3)	14 (4.3)	
Others *	23 (25.3)	53 (22.6)	76 (23.4)	
Severity on Presentation				
Category 1	21 (23.1)	116 (49.6)	137 (42.2)	
Category 2	53 (58.2)	115 (49.1)	168 (51.7)	<0.0001
Category 3	10 (11)	3 (1.3)	13 (4)	
Category 4	5 (5.5)	0 (0)	5 (1.5)	
Category 5	2 (2.2)	0 (0)	2 (0.6)	
Comorbidities				
Diabetes Mellitus	14 (41.2)	20 (58.8)	34 (10.5)	0.071
Hypertension	19 (32.8)	39 (67.2)	58 (17.8)	0.737
Dyslipidaemia	4 (26.7)	11 (73.3)	15 (4.6)	0.9
Ischaemic Heart Disease	2 (15.4)	11 (84.6)	13 (4)	0.301
Stroke	0 (0)	1 (100)	1 (0.3)	0.532
Asthma	3 (42.9)	4 (57.1)	7 (2.2)	0.376
Others ^	12 (44.4)	15 (55.6)	27 (8.3)	0.047
Presence of symptoms				
Yes	70 (76.9)	142 (60.7)	212 (65.2)	0.006
No	21 (23.1)	92 (39.3)	113 (34.8)	

* Sarawakian, Sabahan, Native Malaysian, Nigerian, Egyptian, Arab, Not Stated.
^ Dementia, Major Dispressive Disorder, Eczema, Vitiligo, Chronic Kidney Disease, Rheamatological Disorder, Non Ischemic Cardiac Disease, Malignancy, End Stage Kidney Disease, Gout, Chroic Obstructive Pulmonary Disease, Hypothyroidism, Aplastic Anemia, Benign Prostatic Hyperplasia, G6PD Deficiency, Tuberculous Lymphadinitis, Renovascular Disease, Obstructive Sleep Apnea, Endometrosis, Psoriasis.
'**Student t Test

Figure 2: Total Length of Stay

DISCUSSION

In this study, we observed that those who were treated with HCQ had worse clinical outcome compared with the control group. This result contradicts with few studies done in France and China in the early pandemic that supported the use of HCQ/CQ in COVID-19. Gautret et al from France conducted an open label non-randomized clinical trial where he reported that viral clearance at day 6 was significantly higher in the HCQ treatment group. However, the study was underpowered due to its small sample size (n= 42) and high dropout rate (n=6, 16.7%). In addition, viral clearance may not always translate to clinical improvement, therefore, trial that examine clinical outcome was warranted. (10) Gautret et al recruited another 80 patients treated with HCQ in combination with Azithromycin where they reported that 81.3% of patients had favourable clinical

outcome. Nevertheless, this study does not have a control arm to compare with (11). On the other hand, Chen et al from China reported significant reduction in mean day of fever 3.2 ±1.3 days vs 2.2 ±0.4 days, p=0.0008 and cough 3.1 ±1.5 days vs 2.0 ±0.2 days, p=0.0016 between the control group and patients who received HCQ respectively. In addition, Chen et al observed significant difference in resorption of pneumonia from computed tomography of the chest between patients treated with HCQ and control group, 80.6% vs 54.8%, p=0.0476 respectively. The sample size of this study was small (n=62) and there was no report on patients' clinical outcome although 4 patients from the control group were reported to have progressed into severe disease (12).

Larger scale, well designed, multi-center, randomized controlled trials exhibited contradictory findings. WHO Solidarity Trial, an open label randomized controlled trial of 4 repurposed antiviral drugs namely Remdesivir, HCQ, Lopinavir, and Interferon beta-1a on hospitalized patient with COVID-19 in 30 countries including Malaysia, 947 patients were randomized into HCQ group and 906 patients were in the control group. There was no significant difference in 28 days mortality rate between the HCQ (n=104) and control group (n=84), (rate ratio, 1.19; 95% CI, 0.86-1.59) (13). In the United Kingdom, RECOVERY trial was another open label randomized controlled trial conducted to examine 28 days mortality in patients received HCQ. They found patients treated with HCQ had no statistically significant reduction in 28 days mortality. Death occurred in 27% of the patients in HCQ group versus 25% in the control group. (Risk Ratio, 1.09; 95% CI, 0.97-1.23; p=0.15) (14). A meta-analysis involving 10012 patients showed that patients treated with HCQ had higher all-cause mortality with odd ratio of 1.11, 95% CI: 1.02-1.20. (15) Our result was consistent with both WHO Solidarity and RECOVERY trial where HCQ showed no benefit in patients' clinical outcome.

We observed that all patients who have severe and critical disease (Category 4 and Category 5) on presentation had HCQ initiated (7.7%, n= 7 versus 0%, n=0). In patients with severe and critical disease, there is invasion of SARS-CoV-2 into pneumocyte resulting in release of pro-inflammatory cytokines, this causes hyperinflammatory state leading to further lung damage, cytokine storm, Acute Respiratory Distress Syndrome (ARDS) and multiorgan failure (18). HCQ has weak anti-inflammatory property and this may not be able to halt the progression of cytokine storm leading to unfavourable outcome in patients initiated with HCQ during the course of moderate to severe disease (19). As a result, treatment with more potent anti-inflammatory drug or immunomodulator such as Dexamethasone and Tocilizumab may be needed to show beneficial clinical outcome in more severe hospitalized patients (20, 21). In view of all patients presented with category 4 and

category 5 are in the HCQ cohort, this can be the reason that HCQ group had worse clinical outcome.

In addition, we found that there is statistically significant difference in terms of length of hospital stay between the HCQ cohort and non-HCQ cohort. Generally, patients in HCQ cohort stayed 3 to 4 days longer in hospital compared with non-HCQ group with mean length of stay of 12.45 ±6.872 days versus 8.61 ±4.553 days respectively. RECOVERY trial reported median length of stay of 16 days in patients treated with HCQ versus 13 days in the control group (14). WHO Solidarity trial showed longer length of hospital stay by 1-3 days in the treatment arm as well (13). Patients in the HCQ cohort were hospitalized longer possibly due to more severe disease, and were kept longer in hospital due to isolation requirement by Malaysia national policy even though they were already symptom free. As a result, discharge time is not reflective of duration of illness.

Some studies aim to exploit HCQ antiviral property by initiating HCQ treatment in the earlier course of COVID-19 with the aim of decreasing viral load and preventing damage to the pneumocyte that lead to cytokine storm. Joseph et al conducted a meta-analysis on trials with early initiation of HCQ and post-exposure prophylaxis in outpatient setting, looking into composite of COVID-19 infection, hospitalization and death. This analysis showed 24% risk reduction in composite outcome of COVID-19 infection, hospitalization and death (P=0.025) (22). In our study, mean day of illness for initiation of treatment was 8.05 days (±6.425), Therefore, our study was not able to examine efficacy of HCQ in early course of the disease which may result in favourable outcome.

We found that HCQ appeared to be a safe drug with minimal side effect. Gastrointestinal side effects such as nausea, abdominal discomfort, vomiting and diarrhoea were the most common side effects reported in previous studies (23). However, only one patient was found to have gastrointestinal side effect in our study. Worth to mention, the gastrointestinal symptoms can be presenting symptom of COVID-19, leading to confusion (24). Cardiac arrythmia is one of the main concern in the use of HCQ especially when concomitant arrhythmogenic drugs were administered such as Azithromycin and Remdesivir. (25). We found no such worry in our study. HCQ is metabolized in the liver and have some metabolites cleared by the kidney (26). However, COVID-19 may also contribute to kidney or liver impairment (27). Liver and kidney impairment were observed in three of the patients, but may not solely caused by the drug itself. Nevertheless, HCQ should be used in caution with patients with underlying liver and kidney disease.

One of the limitation of this study is this is a retrospective observational study therefore there is lack of blinding

and randomization. Patients with more severe illness started with other medications such as dexamethasone, methylprednisolone, and lopinavir/ritonavir were excluded from this study. As a result, this cohort consists of patients with milder disease. Patients started with other medication together with HCQ were excluded in this study as well. Thus, we are unable to determine effect of combination therapy. There is also an observed discrepancy between the severity of the disease in both groups, which may have led to a bias result.

CONCLUSION

Consistent with larger trials conducted worldwide, this retrospective cohort study found that HCQ failed to show any benefit in improving clinical outcome or reducing length of hospital stay in patients with COVID-19. Thus, this study further augments the fact that HCQ use in COVID-19 is not encouraged.

ACKNOWLEDGEMENT

REFERENCES

1. World Health Organization- WHO.WHO Coronavirus (COVID-19) Dashboard. Accessed on February 22 2022. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
2. Wen W, Chen C, Tang J, Wang C, Zhou M, Cheng Y, et al. Efficacy and safety of three new oral antiviral treatment (molnupiravir, fluvoxamine and Paxlovid) for COVID-19: a meta-analysis. Annals of Medicine. 2022;54:1516523. doi: 10.1080/07853890.2022.2034936.
3. Maciorowski D, Idrissi SZE, Gupta Y, Medernach BJ, Burns MB, Becker DP, et al. A Review of the Preclinical and Clinical Efficacy of Remdesivir, Hydroxychloroquine, and Lopinavir-Ritonavir Treatments against COVID-19. SLAS Discov. 2020;25(10):1108-1122. doi: 10.1177/2472555220958385.
4. Abolghasemi E, Moosa-Kazemi SH, Davoudi M, Reisi A, Satvat MT. Comparative study of chloroquine and quinine on malaria rodents and their effects on the mouse testis. Asian Pac J Trop Biomed. 2012;2:311–314. doi: 10.1016/S2221-1691(12)60030-6.
5. Misra D, Gasparyan A.Y, Zimba O. Benefits and adverse effects of hydroxychloroquine, methotrexate and colchicine: searching for repurposable drug candidates. Rheumatol Int. 2020;40:1741–1751. doi: 10.1007/s00296-020-04694-2.
6. Shimizu Y, Yamamoto S, Homma M, Ishida N. Effect of chloroquine on the growth of animal viruses. Arch Gesamte Virusforsch. 1972;36(1):93-104. doi: 10.1007/BF01250299.
7. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30:269-271. doi:10.1038/s41422-020-0282-0.
8. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020;71(15):732-739. doi: 10.1093/cid/ciaa237.
9. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a
less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6:16. doi: 10.1038/s41421-020-0156-0.
10. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, 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. doi: 10.1016/j.ijantimicag.2020.105949.
11. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. Travel Med Infect Dis. 2020;34:101663. doi: 10.1016/j.tmaid.2020.101663.
12. Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. MedRxiv. 2020;03.22.20040758. doi: 10.1101/2020.03.22.20040758
13. WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2021;384(6):497-511. doi: 10.1056/NEJMoa2023184.
14. RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020;383(21):2030-2040. doi: 10.1056/NEJMoa2022926.
15. Axfors C, Schmitt AM, Janiaud P, Van't Hooft J, Abd-Elsalam S, Abdo EF, et al. Mortality outcomes with hydroxychloroquine and chloroquine in Covid-19: an international collaborative meta-analysis of randomized trials. Nat Commun. 2021;12(1):2349. doi: 10.1038/s41467-021-22446-z.
16. Coronavirus (COVID-19) Update: FDA revokes emergency use authorization for chloroquine and hydroxychloroquine. Published June 15

2020. Accessed on February 22 2022. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and#:~:text=Today%2C%20the%20U.S.%20Food%20and,clinical%20trial%2-0was%20unavailable%2C%20or

17. COVID-19 management guidelines in Malaysia No 5/2020. Annex 2e. Clinical management of confirmed COVID-19 case in adult and paediatric. Published August 13 2021. Accessed on February 22 2022. Available from: https://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm/ANNEX_2e_CLINICAL_MANAGEMENT_OF_CONFIRMED_COVID-19_CASE_IN_ADULT_AND_PAEDIATRIC_13082021.pdf

18. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506. doi: 10.1016/S0140-6736(20)30183-5.

19. Ornstein MH, Sperber K. The antiinflammatory and antiviral effects of hydroxychloroquine in two patients with acquired immunodeficiency syndrome and active inflammatory arthritis. Arthritis Rheum. 1996;39(1):157-61. doi: 10.1002/art.1780390122.

20. Biran N, Ip A, Ahn J, Go RC, Wang S, Mathura S, et al. Tocilizumab among intensive care unit COVID-19 patients: a multi-center observational study. Lancet Rheumatol. 2020;2(10):e603-e612. doi: 10.1016/S2665-9913(20)30277-0.

21. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021;384(8):693-704. doi: 10.1056/NEJMoa2021436.

22. Ladapo JA, McKinnon JE, McCullough PA, Risch H. Randomized controlled trials of early ambulatory hydroxychloroquine in the prevention of COVID-19 infection, hospitalization, and death: meta-analysis. medRxiv. 2020.09.30.20204693; doi: 10.1101/2020.09.30.20204693

23. Srinivasa A, Tosounidou S, Gordon C. Increased incidence of gastrointestinal side effects in patients taking hydroxychloroquine: A brand-related issue? J Rheumatol. 2017;44(3):398. doi: 10.3899/jrheum.161063.

24. Zhang J, Garrett S, Sun J. Gastrointestinal symptoms, pathophysiology, and treatment in COVID-19. Genes Dis. 2021;8(4):385-400. doi: 10.1016/j.gendis.2020.08.013.

25. Costedoat-Chalumeau N, Hulot JS, Amoura Z, Leroux G, Lechat P, Funck-Brentano C et al. Heart conduction disorders related to antimalarials toxicity: An analysis of electrocardiograms in 85 patients treated with hydroxychloroquine for connective tissue diseases. Rheumatology. 2007;46(5):808–10. doi: 10.1093/rheumatology/kel402.

26. .Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: Implications for rheumatology. Nat Rev Rheumatol. 2020;16(3):155–66. doi: 10.1038/s41584-020-0372-x.

27. Rismanbaf A, Zarei S. Liver and Kidney Injuries in COVID-19 and Their Effects on Drug Therapy; a Letter to Editor. Arch Acad Emerg Med. 2020;8(1):e17. Avilable from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7075271/pdf/aaem-8-e17.pdf.