International Invention of Scientific Journal
Online ISSN: 2457-0958
Available Online at https://iisj.in **Volume 8, Issue 04 (October-November-December)|2024**|Page: 804-817
Review Paper-Medical Sciences

Hydroxychloroquine Therapeutic effects on COVID19: a systematic review and meta-analysis

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Article Received: 20-September -2024 Revised: 10-October-2024 Accepted: 30-October-2024

ABSTRACT:
Objective: To summarize, and prove almost the benefits and hurts of hydroxychloroquine (HCQ) or chloroquine for the treatment or prophylaxis of coronavirus infection 2019 (COVID-19).
Designs: A comprehensive electronic search of the terms relevant to this review to identify the relevant studies.
Setting: Systematic review and meta-analysis study.
Subjects: Articles focusing on HCQ and prophylaxis of COVID-19, published up to Jan 2021.
Intervention: Retrieved articles were subtly studied. Data obtained included the mutual relationship between the HCQ SARS-CoV-2.
Main Outcome Measure: the adequacy of security results from hydroxychloroquine or chloroquine are utilized in any setting in licenses with suspected COVID-19 or at hazard for SARS-CoV-2 disease.
Results: A add-up to 824 articles were screened, and 14 clinical considerations with an add-up to test measure of 5548 (2874 cases and 2674 controls) patients were included. A few clinical ponders illustrated great virological and clinical results with HCQ alone o in COVID-19 patients, even though the thinks about had significant methodological restrictions. A few of the other things about appeared negative comes about with HCQ treatment besides the hazard of unfavorable responses.
Conclusion: Prove the benefits and hurts of utilizing hydroxychloroquine or chloroquine to treat COVID-19 is exceptionally frail and clashing. Be that as it may, clinical utilization ought to either follow the Observed Crisis Utilize of Unregistered Intercessions (MEURI) system or be morally affirmed as a trial as expressed by the World Wellbeing Organization. Security information and information from high-quality clinical trials are direly required.

Keywords: hydroxychloroquine, severe acute respiratory syndrome coronavirus 2, COVID-19, MEURI.

INTRODUCTION:

The first case of the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2, formerly known as 2019-nCoV) was distinguished in Wuhan, which COVID-19 has globally affected about ten million people worldwide [1]. Severe Acute Respiratory Syndrome (SARS) (2003), influenza virus with the H1N1 subtype (2009), Middle-East Respiratory Syndrome (MERS) (2012), and Ebola virus (2014) were observed in the past twenty years which was the chief cause of the global predicaments among people [2]. Although COVID-19 is one of the potential viruses of coronaviruses, and this virus is akin to more of the illnesses such as SARS and MERS, infection symptoms include fever, chills, cough, sore throat, myalgia, nausea and vomiting, and diarrhea [3]. It worth mentioning that infecting with such a virus is dangerous for individuals with a history of underlying diseases and would experience worse outcomes [4]. Tough disease cases manage to heart, respiratory failure, acute respiratory syndrome, or even death [5]. Despite the similarity of COVID-19 with the previous ones, severe acute respiratory syndrome (SARS; 2002-2003) and the

Middle-East respiratory syndrome (MERS; 2012-ongoing), but there are differences [6]. The SARS-CoV emerged from the bats and was transmitted to humans through the intermediate host of palm civet cats, while A MERS-CoV ancestral virus was isolated from dromedary camels[7, 8]. The common symptoms among 3 viral infections were fever, cough, and subsequent respiratory failure, leading to a poor disease outcome in patients with a history of cardiovascular disease, respiratory problems, cancer, diabetes, and infection [9]. Furthermore, age and sex are the other significant factors in these infections since it has been found that infecting more males than females refers to an immunological advantage for females and the role of the X chromosome in the innate and adaptive immune response [4]. A complete blood test assesses C-reactive protein and lactate dehydrogenase levels to diagnose infection in individuals and recommended a chest computed tomography (CT) scan for further examination [10]. Finally, reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay is used to confirm the infection [11]. Based on the World Health Organization (WHO) information at the time of the COVID-19 With SARS and MERS, overall, 8096 cases with 774 deaths were reported after the epidemic. The case fatality ratio (CFR) was 9.6%. The MERS outbreak involved 27 countries, with 2494 confirmed cases and 866 associated deaths (case-fatality rate: 34.4%). While SARS and MERS mortality rates were higher than COVID-19 but COVID-19 transmitted more rapidly than SARS and MERS [12]. After the last report was released in worldwide (April 2, 2020), the number of death was 47264 among 936865 confirmed cases, the overall number of COVID-19 cases, including those unrecognized due to mild and asymptomatic symptoms or lack of the still-insufficient capacity for testing, would be much higher than obvious [6]. The transmission of MERS-CoV and SARS-CoV by healthcare setting has been mentioned as the secondary cases [13]. Similarly, almost individuals diagnosed with COVID-19 were related to healthcare.

Hydroxychloroquine (HCQ) plays a weak base, with its non-protonated component crossing the cell and transforming into protonated form. It is located in acidic organelles (endosome, lysosome, and Golgi vesicles) and interferes with the entry of viruses associated with pH, thus inhibiting their entire replication cycle. The increased pH induced by chloroquine also disrupts proteases and glycosyl-transferases' function in the post-translational processing of envelope glycoproteins in the Golgi [14]. To initiate the process of entry into a target cell, conjugate the coronavirus surface protein spike (S) to angiotensin-converting enzyme 2 (ACE2) on the cell membrane and the host cell protease (activated during acidification of the endosome) trigger the S-protein cleavage that leads to viral infectivity. As previously mentioned, chloroquine has shown therapeutic activity against SARS in cell culture through acidification inhibition, and viral replication stalled [15]. Because of the similarities between the external covid-19 receptor subdomain and SARS, the angiotensin-converting enzyme 2 (ACE2), the SARS receptor, is likely to be a covid-19 receptor and be used in cell entry [16]. This study examines and systematically reviews and analyzes the literature and their reported results related to the impacts of a critical drug (chloroquine) with treatment COVID-19 cases.

Null hypothesis:

There is no consensus on the effectiveness of hydroxychloroquine on Covid-19 patients.

METHODOLOGY:

Search strategy and selection criteria:

This study used a simple systematic review protocol following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Fig. 1).

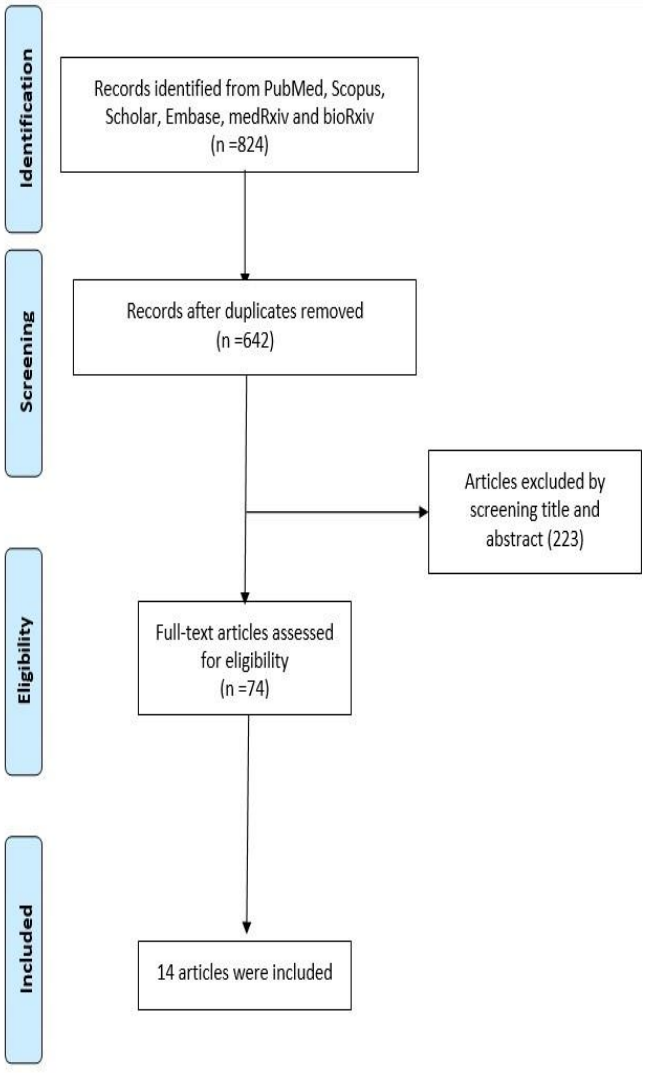


Figure 1: Looking at databases found flow diagram of the literature review process: A adds up to 824 articles. After evacuating duplication, 642 articles were screened by title and unique. At that point, 74 articles were surveyed for full-text, and 14 articles were at long last included.

We used a systematic literature search in diverse databases as follow: PubMed, Scopus, Scholar, Embase, medRxiv, and bioRxiv in January 2021 using the following terms: "SARS-CoV-2", "COVID-19", "coronavirus", "chloroquine", and "population", Desktop 1.17.11 software (London, UK) to remove duplicates. The title and abstract of all manuscripts were checked by two independent reviews (M.CH and R.K) and research reports which reported the prevalence of anti-SARS-CoV-2 serum antibodies in the 'general population' (i.e., randomly-selected people of different ages, occupations, educational and ethnic backgrounds, socioeconomic status, living in a defined geographical region, whose prior COVID-19 status was unknown). Articles were prohibited in case they (1) included suspected, affirmed, or hospitalized COVID-19 patients; (2) were performed in the at-risk populace (e.g., health-care laborers) or people with known infections (e.g., cancer or dialysis patients); (3) recorded predominance based on clinical sign, computed tomography filter or PCR; (4) were comparative considers of demonstrative strategies; (5) utilized information sets that covered with those of other articles; (6) were case reports or case considers; or (7) were publications, commentaries, surveys or efficient audits.

Data Extraction:

After the screening of published articles, the relevant data from eligible studies were extracted by three independent reviews, and in order to agree and disagreement had been used the fourth review. The different information regarding the type of article, study type, patient demographics (age, gender, exposure, etc.), symptoms, chest imaging, clinical management (treatment, respiratory support), and clinical outcomes was uncovered in an excel sheet template (version 2016; Microsoft Corporation, Redmond, USA).

Data Analysis:

The frequencies and extents of patient's characteristics were surveyed. Logit and twofold arcsine change strategies were utilized in comparative meta-analysis. The pooled predominance of statistic variables, clinical characteristics, and results were calculated with 95% certainty interims, and woodland plots were produced utilizing R factual program adaptation 3.6.3. A random-effects demonstration was utilized, which may be a more traditionalist approach, considering the changeability of epidemiological and clinical characteristics. As it considered with the fair chance of bias, and grown-up populaces were included within the meta-analysis.

LITERATURE REVIEW:

Some surveys have been conducted in this field throughout the world. Rahimi *et al.*[17] l assessed the effect of hydroxychloroquine on COVID-19 prevention in cancer patients. Their findings showed thehigh efficacy of hydroxychloroquine as a drug to reduce the progress and clinical signs of the COVID-19. Self *et al*.[18] carried out a randomized clinical trial that included 479 hospitalized adults with respiratory symptoms of COVID-19. They found that the distribution of the day 14 clinical status score (measured using a 7-category ordinal scale) was not significantly different for patients randomized to receive hydroxychloroquine compared with placebo (adjusted odds ratio, 1.02). In another survey, Reis *et al*.[19] carried out a research on 685 patients and showed that the rates of COVID-19–associated hospitalization in patients treated with hydroxychloroquine were not significantly different compared with those who received placebo. Rentsch *et al*.[20] reported that of 194 637 people with rheumatoid arthritis or systemic lupus erythematosus, 30 569 (15·7%) received two or more prescriptions of hydroxychloroquine. They showed that there were 547 COVID-19 deaths, 70 among hydroxychloroquine users. Estimated standardised cumulative COVID-19 mortality was 0·23% (95% CI 0·18 to 0·29) among hydroxychloroquine users and 0·22% (0·20 to 0·25) among hydroxychloroquine non-users. They found no evidence of a difference in COVID-19 mortality among people who received hydroxychloroquine for treatment of rheumatological disease before the COVID-19 outbreak in England. In another research[21], death within 28 days occurred in 421 patients (27.0%) in the hydroxychloroquine group and in 790 (25.0%) in the usual-care group (rate ratio, 1.09; 95% confidence interval [CI], 0.97 to 1.23; P=0.15). The results suggest that patients in the hydroxychloroquine group were less likely to be discharged from the hospital alive within 28 days than those in the usual-care group (59.6% vs. 62.9%; rate ratio, 0.90; 95% CI, 0.83 to 0.98).

RESULTS:

Generally, 824 articles were recognized by mining information base and manual looking, and after evacuating comparable of articles, almost 642 articles were cleared out. Within the screen title and theoretical organize, 223 full-text articles were chosen for further evaluation, and within the following stage, 74 articles were avoided concurring the choice criteria. At long last, arrange of the meta-analysis survey article accounted for 14 articles [22-35] (Figure 1). Among the distributed clinical considers, Gauret et al. [30, 36] and Chen *et al*. [37]

have illustrated exceptionally great virological and clinical results with HCQ treatment alone or combined with azithromycin. Million *et al*. [30] have moreover illustrated great virological and clinical results with HCQ treatment. Molina et al. have appeared negative comes about with HCQ treatment [31]. Among the non-peer-reviewed ponders included from preprint servers, Chen et al. have illustrated great virological and clinical results with HCQ treatment. The comes about of Magagnoli *et al*. [27], Mahévas *et al*. [28], Tang *et al*. [34], and Ramireddy *et al*. [38] were negative or dubious. Moreover, Geleris *et al*. [25] detailed no critical impact of HCQ on intubation or passing in COVID-19 patients. Within the ponders of Gauret *et al*. [30, 36], Chen *et al*. [37], and Million *et al*. [25], HCQ was found to be secure with gentle antagonistic responses, such as sickness, spewing, and transitory unusual liver capacities. Molina *et al*. [31] and Mercuro *et al*. [29] have detailed QT prolongation in the electrocardiogram (ECG) related to HCQ treatment (Table 1).

Table 1. Baseline Characteristics of articles Assessing the therapeutic effects of the hydroxychloroquine on new sars-covid19

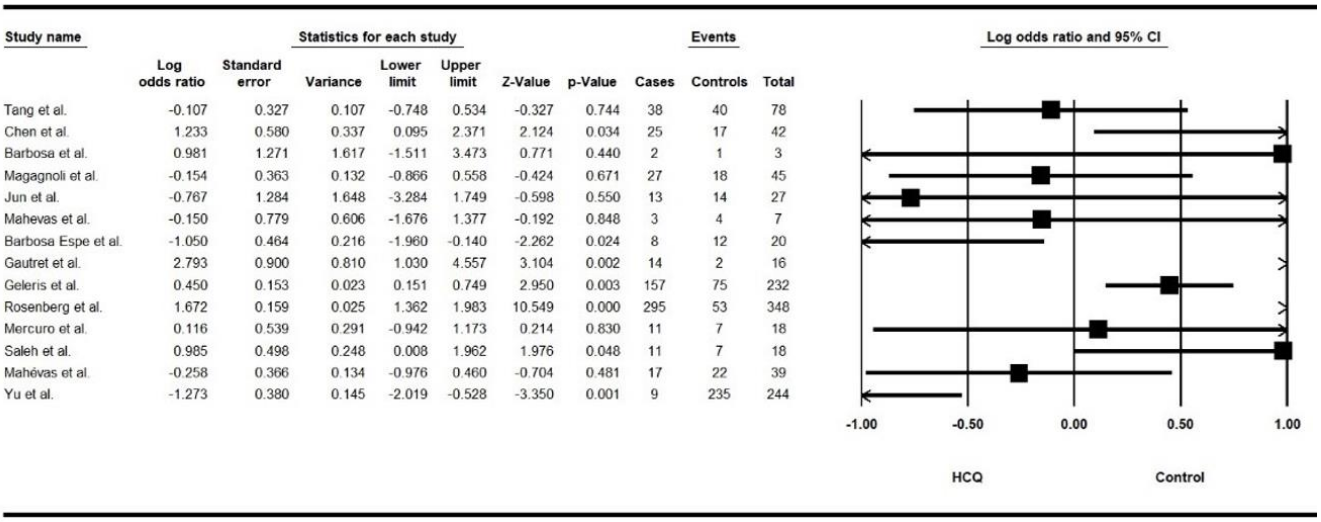
Author,Year	Study design	Country	Mean Age	Patient N	Case group	Control group	HCQ dose/day X Days	Primary outcome	Secondary outcome	Primary Improvement outcome	Secondary Improvement outcome
Tang et al, 2020	RCT	China	46	150	75	75	1200 mg/d X 3D, followed by 800 mg/d X 2 wks (I) or 3 wks (II)	Viral load by RTPCR +vs. -at day 28	Clinical symptoms, normalization of laboratory parameters and chest radiology	NO	NO
Chen rt al, 2020	RCT	China	44.7	62	31	31	400 mg/d X 5D	Time to clinical recovery and improvement of pneumonia in chest CT	NR	YES	NR
Barbosa et al, 2020	qRCT	USA	62.7	63	32	31	800 mg/d X 1-2D followed by 200 - 400 mg OD X 3-4D	Need to escalate respiratory support and rate of intubation at day 5	Change in lymphocyte count, NLR, and mortality	NO	NO
Magagnoli et al, 2020	RET	USA	68	368	210	158	NR	Need for MV and death from any cause	Death in patients on MV	NO	NO
Jun et al, 2020	RCT	China	NR	30	15	15	400 mg/d X 5D	Viral load by RTPCR +vs. -at day 7	NR	NO	NR
Mahevas et al, 2020	RET	France	60	181	84	97	600 mg/d X 7D	ICU transfer or death	All-cause	NO	NO

								from any cause at day 7	mortality at day 7, Occurrence of ARDS within 7 D		
Gautret et al, 2020	PRO	France	52.1	80	80	0	600 mg/d X 10D + AZ 500 mg on day 1 and 250 mg/d X 4D	Need for O2 therapy or ICU admission	Viral load, length of hospital stays	YES	YES
Geleris et al, 2020	PRO	USA	NR	1376	1376	0	600 mg / d X 1D, 400 mg /d X 5D	NR	NR	NO	NO
Rosenberg et al, 2020	RET	USA	63	1438	143	0	400 mg/d X 10D + AZ 500 mg/X 1D + 250 mg 2- 5 D	mortality	cardiac arrest and abnormal electrocardiogram findings	NO	NO
Mercuro et al, 2020	RET	USA	60.1	90	53	37	400 mg of hydroxychloroquine 2X 1D, 400 mg/ 1X 2D	pneumonia, Change in QT interval after receiving hydroxychloroquine with or without azithromycin; occurrence of other potential adverse drug events.	NR	NO	NO
Saleh et al, 2020	PRO	USA	58.5	201	201	0	500 mg /2X 1D followed by 500 mg /1X 4D, hydroxychloroqui	QT prolongation resulting in Torsade de pointes.	QT prolongation, the need to prematurely discontinue any of	NR	NR

							ne 400 mg /2X 1D followed by 200 mg /2X 4D, and azithromycin 500 mg/ X 5D		the medications due to QT prolongation, and arrhythmogenic death		
Yu et al, 2020	PRO	China	NR	568	568	0	200 mg/d X 7-10D	mortality	NR	NO	NO

Mild/moderate Cases: I; Sever Cases: II; NR: Not Report; RCT: Randomized clinical trial; RET: Retrospective study; PRO: Prospective-observational study.

HCQ treatment was related to genuine antagonistic responses, such as passing, QT prolongation, first-degree atrioventricular square, diarrhea, and obscured vision within the non-peer-reviewed ponders included from preprint servers [27, 28, 34, 38] (Figure 2).



Study name	Log odds ratio	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Cases	Controls	Total
Tang et al.	-0.107	0.327	0.107	-0.748	0.534	-0.327	0.744	38	40	78
Chen et al.	1.233	0.580	0.337	0.095	2.371	2.124	0.034	25	17	42
Barbosa et al.	0.981	1.271	1.617	-1.511	3.473	0.771	0.440	2	1	3
Magagnoli et al.	-0.154	0.363	0.132	-0.866	0.558	-0.424	0.671	27	18	45
Jun et al.	-0.767	1.284	1.648	-3.284	1.749	-0.598	0.550	13	14	27
Mahevas et al.	-0.150	0.779	0.606	-1.676	1.377	-0.192	0.848	3	4	7
Barbosa Espe et al.	-1.050	0.464	0.216	-1.960	-0.140	-2.262	0.024	8	12	20
Gautret et al.	2.793	0.900	0.810	1.030	4.557	3.104	0.002	14	2	16
Geleris et al.	0.450	0.153	0.023	0.151	0.749	2.950	0.003	157	75	232
Rosenberg et al.	1.672	0.159	0.025	1.362	1.983	10.549	0.000	295	53	348
Mercuro et al.	0.116	0.539	0.291	-0.942	1.173	0.214	0.830	11	7	18
Saleh et al.	0.985	0.498	0.248	0.008	1.962	1.976	0.048	11	7	18
Mahévas et al.	-0.258	0.366	0.134	-0.976	0.460	-0.704	0.481	17	22	39
Yu et al.	-1.273	0.380	0.145	-2.019	-0.528	-3.350	0.001	9	235	244

Figure 2: Risk of an outbreak among COVID-19 patients uncovered to HCQ compared to non-HCQ (standard care).

DISCUSSION:

COVID 19 is the most dangerous among illnesses in 2020 that s causing significant disruption to health systems [39, 40]. Our review explored the general population's mental health status and its predictive factors amid the COVID-19 pandemic. Generally, there is a higher prevalence of symptoms of adverse psychiatric outcomes among the public when compared to the prevalence before the pandemic. Additionally, In this research, we evaluated an important drug (chloroquine) used to treat patients. The ponders of Chen *et al*. [37] and Gautret *et al*. [36] were underpowered. Chen *et al*. [37] included patients with mellow indications as it were, and they were concomitantly treated with other antivirals.

To begin with, Gautret et al. [31] did not randomize the patients or incorporate drop-outs within the last examination. There were heterogeneities in terms of the viral stack between the two bunches at standard, and the agents veered off from the enrolled convention in terms of the result measures. Clinical outcomes, even though enormously imperative, were not detailed. Within the moment ponder, Gautret *et al*. [30] not one or the other included a control arm nor said the qualification criteria. Moreover, within Geleris *et al*. [25], the HCQ-treated patients were more severely ill at the pattern. Within the ponder of Chen *et al*.[37], there was a slight improvement in body temperature and hack with a better measurement of HCQ. In any case, the endpoints indicated within the distributed convention varied from those detailed, the comes about the low-dose HCQ bunch were not detailed, and the trial was rashly ended [41]. The most significant observational consider of Million et al., with a test estimate of 1061 patients, did not have a control arm [30]. Assist, no clinically significant medium- or long-term follow-up information are detailed in any of these considers [25, 38]. Another major factor to be considered is that exceptionally few ponders have centered on the security angle of HCQ within the treatment of COVID-19.

Hydroxychloroquine and chloroquine have picked up a part of steam within the restorative field and media for their potential viability against COVID-19. Hydroxychloroquine has immunomodulatory properties and was initially created as an antimalarial medicate with encouraging applications in patients with rheumatoid joint pain and systemic lupus erythematosus [42]. *In vitro* thinks that hydroxychloroquine has also appeared antiviral properties; it is as far as anyone knows anticipates COVID-19 related ARDS [43, 44]. The treatment of COVID-19 positive patients with hydroxychloroquine has been met with discussion, as there have been no expansive multicenter randomized control trials to bolster its utilize. Up to this point, there is a need for measurably critical diminishment in horribleness or mortality in COVID-19 patients who have experienced hydroxychloroquine trials. The side impacts of 4-Aminoquinolones are known to be dose-dependent expanded dangers for retinopathy, methemoglobinemia, and gastrointestinal, renal, and poisonous cardiac quality [44]. Borba et al. consider that guys matured 50 with extreme COVID indications and heart infection are at a tall chance of creating hydroxychloroquine-related cardiac complications such

as QT prolongation at higher dosages of hydroxychloroquine [45]. The considers by Tang *et al*. [46] and Chen *et al.* [37] appeared more prominent hydroxychloroquine -related GI side impacts as well. In a post-marketing ponder by the Nourishment and Sedate Organization (FDA), it was too appeared that the utilize of 4-Aminoquinolones expanded rates of cardiac arrhythmias, ventricular tachycardia, fibrillation, and torsades de pointes. Their examination moreover famous unfavorable cardiac occasions combined with the utilization of other QT-prolonging solutions [47, 48]. Additionally, this meta-analysis underpins that hydroxychloroquine-treated patients are more likely to have unfavorable side impacts. Moreover, it shows that treatment with hydroxychloroquine features a casualty rate of around 2.5 higher than with the control group. The non-randomized ponder performed by Gautret et al. within the South of France, including an add-up to 36 youthful patients with positive PCR test, comes about and milder COVID-19 infection with no progressed comorbid therapeutic conditions. A 50% lessening in the viral stack was famous at one week with a moo dosage of hydroxychloroquine [36]. This consider was not fueled to identify mortality results. Many researchers [37, 49, 50] considered females with a middle-age of 45 and mellow COVID-19 related upper respiratory/pneumonia indications without co-existing co-morbid therapeutic malady. Patients were expressed to have moved forward time to a clinical determination within the hydroxychloroquine treatment arm [3, 37, 50, 51]. These appear to be in line with the meta-analysis' of a slight illness change in COVID-19 patients treated with hydroxychloroquine than the controls. Simultaneously, the rate of patients treated with chloroquine drugs was the lowest percentage of mortality rates. Moreover, later considers appear a sex dissimilarity, in that females appear superior results compared to comparative male cohorts [51]. This sexual orientation difference is seen in a later ponder that famous male patients with progressed age, or different comorbid therapeutic conditions are at higher mortality rates [3, 51]. The ponders in this meta-analysis did not incorporate these high-risk patients with essential complex co-morbid therapeutic conditions, severe cases of COVID-19, ARDS, or primary care persistent populaces [52]. However, infections may causes several complication and threats on human health [53-60], but several treatment options have been developed against them.

CONCLUSION:

There is am inadequate clashing evidence on the benefits and disadvantages of utilizing hydroxychloroquine to treat COVID-19. There is an adequate pre-clinical method of reasoning and proof concerning the adequacy of chloroquine for treatment of COVID-19 and proof of security from long-time use in clinical hone for other signs to legitimize clinical research on the subject. The current circumstances legitimize the prioritization of a moral survey of pondering propositions over others, less squeezing, and inquiring about subjects. As such, it is outlandish to decide the adjustment of benefits to hurts. There are no evaluations of hydroxychloroquine or chloroquine for prophylaxis against COVID-19. Even though the master conclusion may back the use of chloroquine, the clinical utilization of this sedate in patients with COVID-19 ought to follow the MEURI system or after moral endorsement as a trial expressed. The randomized controlled trials generally had a choice, execution, and discovery inclinations, whereas the observational considers had comparability, presentation, and result predispositions transcendently.

ACKNOWLEDGMENTS:

We want to thank the Department of Emergency Medicine, Faculty of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran

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