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# Safety profile of chloroquine and hydroxychloroquine: a disproportionality analysis of the FDA Adverse Event Reporting System database

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**Abstract. – OBJECTIVE: The present study aims to identify potential safety signals of chloroquine (CQ) and hydroxychloroquine (HCQ), over the period preceding their repurpose as COVID-19 treatment options, through the analysis of safety data retrieved from the FDA Adverse Event Reporting System (FAERS) pharmacovigilance database.**

**MATERIALS AND METHODS: We performed a disproportionality analysis of FAERS data between the first quarter of 2004 and December 2019 using the OpenVigil2.1-MedDRA software. Disproportionality was quantified using the reporting odds ratio (ROR) and its 95% confidence interval (CIs). The reported mortality of CQ and HCQ was also investigated.**

**RESULTS: The dataset contained 6,635,356 reports. Comparison of the RORs revealed significant differences between CQ and HCQ for the following adverse events: cardiomyopathy, cardiac arrhythmias, retinal disorders, corneal disorders, hearing disorders, headache, hepatic disorders, severe cutaneous reactions, musculoskeletal disorders, and cytopenia. Only CQ was associated with psychotic disorders, suicide, self-injury, convulsions, peripheral neuropathy, and decreased appetite. In multivariable logistic regression, death was more frequently associated with CQ use, advanced age, male sex, co-reported suicide and self-injury, cardiomyopathy, cardiac arrhythmias, and decreased appetite.**

**CONCLUSIONS: Our results confirm previously published evidence and suggest that HCQ has a safer clinical profile compared to CQ, and thus could serve as the drug of choice for future therapeutic purposes.**

*Key Words:*
Safety, Chloroquine, Hydroxychloroquine, Disproportionality analysis, FAERS.

## Introduction

In the era of the COVID-19 pandemic, there is an urgent need to identify new drugs as well as repurpose older drugs that could effectively treat or prevent disease spread. Chloroquine (CQ) and its structural analogue hydroxychloroquine (HCQ) have been used for more than 50 years as the primary and most successful drugs against malaria and certain autoimmune diseases. Based on their inhibitory action on the endosomal-lysosomal acidification process and their anti-inflammatory and immunomodulatory effects, CQ and HCQ have been investigated as potential treatments of COVID-19.

On March 28th,2020 the FDA issued an Emergency Use Authorization that allowed the

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emergent use of chloroquine phosphate and hydroxychloroquine sulfate in the treatment of COVID-19[1].On April 23, 2020 the European Medicines Agency (EMA) released a public health statement that acted as a reminder of the risk of serious, in some cases fatal, arrhythmias associated with CQ or HCQ, particularly when these drugs were taken at high doses or in combination with azithromycin[2]. One day later, on April 24, 2020 FDA released a drug safety communication recommending the use of HCQ or CQ for COVID-19 only in hospital and under clinical trial settings[3]. On July 4, 2020 the WHO supported the recommendation of the Solidarity Trial's International Steering Committee to discontinue the hydroxychloroquine arm, based on results suggesting that HCQ *vs.* standard-of-care did not decrease mortality in hospitalized patients with COVID-19. Further studies[4,5] on the prophylacticor therapeutic use of CQ[6] and mainly HCQ[7-11] suggested no effect in terms of clinical status or mortality, while several concerns emerged, including severe cardiac complications, during the use of CQ or HCQ in patients with COVID-19[12,13].

The use of already available human safety data is of utmost importance to evaluate the risks and benefits associated with CQ. Pharmacovigilance databases, such as the US Food and Drug Administration Adverse Event Reporting System (FAERS), contain valuable real-world data on suspected adverse drug reactions. The aim of the present study was to identify potential safety signals of CQ and HCQ use, during the period preceding their repurpose as COVID-19 treatment options, using a disproportionality analysis of FAERS data between the first quarter of 2004 and December 2019.

## Materials and Methods

### Database

The FAERS is a pharmacovigilance database that includes U.S. and international data on suspected adverse drug reactions and relevant administrative information, patient demographics, information about drug regimens, and patient outcomes[14]. OpenVigil2.1-MedDRA software is an open data-mining tool that incorporates the MedDRA terminology (Introductory Guide for Standardized MedDRA Queries (SMQs) Version 22.0.; 2019) and facilitates the access to and analysis of clean (verified and normalized drug names) FAERS data, as well as access to individual reports and counts of safety reports meeting specific criteria. The OpenVigil2.1-MedDRA software was used to retrieve reports submitted between the first quarter of 2004 and December 2019 (period available via OpenVigil2.1-MedDRA). Our team has published several papers using the methodology of disproportionality analysis on datasets derived from the FAERS database, and recently systematically reviewed this methodology on studies conducted among the most important spontaneous reporting databases: the databases of the World Health Organization (VigiBase), of the European Medicines Agency (EudraVigilance), and the FAERS[15].

### Case/Non-Case Analysis of the Safety Profile of CQ and HCQ

First, we conducted a case/non-case analysis to investigate the safety profile of CQ and HCQ. The following list of adverse events was selected after inspection of the Summary Product Characteristics of both drugs: cardiomyopathy, cardiac arrhythmias, convulsions, headache, extrapyramidal symptoms, peripheral neuropathy, musculoskeletal disorders, depression, psychotic disorders, suicide and self-injury, corneal disorders, retinal disorders, hearing and vestibular disorders, gastrointestinal symptoms, hepatic disorders, decreased appetite, lactose intolerance, hypoglycemia, DRESS, hypersensitivity and hematopoietic cytopenia. The above adverse events were matched to MedDRA terms, with priority given to standardized MedDRA Queries (SMQs) and higher-level terms (Table I). Reports with the above events associated with CQ or HCQ were defined as cases while other events were defined as non-cases.

Disproportionality analysis was performed to detect a safety signal for each of the investigated adverse events and any association with either CQ or HCQ. Disproportionality was quantified using the reporting odds ratio (ROR) and its 95% confidence interval (CIs). ROR estimates the frequency of the examined adverse event co-reported with the drug of interest and compared to all other drugs in the database. Disproportionality signals were defined when the lower boundary of the 95% CI of the ROR was greater than one and the number of reports was higher than three[16]. RORs and their confidence intervals were calculated with OpenVigil2.1-MedDRA.

**Table I.** Selected MedDRA terms used.

| Events | Selected MedDRA terms |
|---|---|
| Arthritis | Arthritis (SMQ† narrow scope) |
| Cardiac Arrhythmias | Arrhythmia related investigations, signs and symptoms (SMQ narrow scope) |
| | Bradyarrhythmia terms, nonspecific (SMQ narrow scope) |
| | Conduction defects (SMQ narrow scope) |
| | Disorders of sinus node function (SMQ narrow scope) |
| | Cardiac arrhythmia terms, nonspecific (SMQ narrow scope) |
| | Supraventricular tachyarrhythmias (SMQ narrow scope) |
| | Tachyarrhythmia terms, nonspecific (SMQ narrow scope) |
| | Ventricular tachyarrhythmias (SMQ narrow scope) |
| Cardiomyopathy | Cardiomyopathy (SMQ narrow scope) |
| Convulsions | Convulsions (SMQ narrow scope) |
| Corneal disorders | Corneal disorders (SMQ narrow scope) |
| Decreased appetite | Decreased appetite (PT‡) |
| Depression | Depression (SMQ narrow scope) |
| Extrapyramidal symptoms | Akathisia (SMQ narrow scope) |
| | Dyskinesia (SMQ narrow scope) |
| | Dystonia (SMQ narrow scope) |
| | Parkinson-like events (SMQ narrow scope) |
| Gastrointestinal symptoms | Gastrointestinal nonspecific symptoms and therapeutic procedures (SMQ narrow scope) |
| Haematopoietic cytopenia | Haematopoietic cytopenias affecting more than one type of blood cell (SMQ narrow scope) |
| | Haematopoietic erythropenia (SMQ narrow scope) |
| | Haematopoietic leukopenia (SMQ narrow scope) |
| | Haematopoietic thrombocytopenia (SMQ narrow scope) |
| Headache | Headache NEC. (HLT§) |
| Hearing and vestibular disorders | Hearing impairment (SMQ narrow scope) |
| | Vestibular disorders (SMQ narrow scope) |
| Hepatic disorders | Cholestasis and jaundice of hepatic origin (SMQ narrow scope) |
| | Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ narrow scope) |
| | Hepatitis, non-infectious (SMQ narrow scope) |
| | Liver related investigations, signs and symptoms (SMQ narrow scope) |
| | Liver-related coagulation and bleeding disturbances (SMQ narrow scope) |
| Hypersensitivity | Hypersensitivity (SMQ narrow scope) |
| Hypoglycaemia | Hypoglycaemia (SMQ narrow scope) |
| Lactose intolerance | Lactose intolerance (PT) |
| Malaria | Malaria (PT) |
| Musculoskeletal disorders | Muscle atrophy (PT) |
| | Muscular weakness (PT) |
| | Musculoskeletal discomfort (PT) |
| | Musculoskeletal pain (PT) |
| | Myalgia (PT) |
| | Neuromyopathy (PT) |
| Peripheral neuropathy | Peripheral neuropathy (SMQ narrow scope) |
| Psychotic disorders | Psychosis and psychotic disorders (SMQ narrow scope) |
| Retinal disorders | Retinal disorders (SMQ narrow scope) |
| Severe cutaneous reactions | Severe cutaneous adverse reactions (SMQ narrow scope) |
| | Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ narrow scope) |
| Suicide and self-injury | Suicide and self-injury (SMQ narrow scope) |
| Systematic lupus erythematosus | Systemic lupus erythematosus (SMQ narrow scope) |

†Standardized MedDRA Querie.

### *Reporting Death in CQ and HCQ Reports*

Further, we investigated the reported mortality of CQ and HCQ. The sample consisted of reports mentioning the use of CQ or HCQ and the data was extracted using OpenVigil2.1-MedDRA, while duplicates were excluded. Multivariable logistic regression was conducted using the outcome of the report (death or not) as the dependent variable and as the presence of one of the above MedDRA terms (including arthritis, malaria, sys-

tematic lupus), age, sex, reporting year, reporting country (US or not US) and drug (CQ or HCQ) as the independent variables. Complete case analysis was conducted and reports with missing data concerning age, sex, reporting year, reporting country, drug name or outcome were excluded. Alpha was set at two-sided 0.05 and analysis was performed in R version 3.6.1.

## Results

The dataset contained 6,635,356 reports submitted in FAERS between the first quarter (Q1) of 2004 and December (Q4) 2019. CQ was identified in 942 (0.014%) reports and HCQ in 25,862 (0.390%). Disproportionality signals and RORs are reported in Table II and Figure 1. Based on the signal results, both CQ and HCQ were associated with reported cardiomyopathy, cardiac arrhythmias, retinal disorders, corneal disorders, hepatic disorders, hearing and vestibular disorders, severe cutaneous reactions, headache, musculoskeletal disorders and hematopoietic cytopenia. In addition, CQ was significantly associated, showing RORs indicative of a safety signal, with psychotic disorders, suicide and self-injury, convulsions, peripheral neuropathy and decreased appetite, while no signal was detected for HCQ and these adverse events. However, HCQ was associated with reported hypersensitivity and gastrointestinal symptoms.

Based on the comparison of RORs, significant differences were observed between CQ and HCQ indicating a favorable safety profile of HCQ for most of the selected adverse events: cardiomyopathy (22.2 *vs.* 3.2 for CQ and HCQ respectively), cardiac arrhythmias (CQ: 7.6 *vs.* HCQ: 1.2), retinal disorders (CQ:12.6 *vs.* HCQ:4.2), corneal disorders (CQ:8.7 *vs.* HCQ:1.8), hearing and vestibular disorders (2.4 *vs.* 1.3), headache (1.7 *vs.* 1.5), hepatic disorders (CQ: 3.1 *vs.* HCQ: 1.8), severe cutaneous reactions (2.9 *vs.* 2.5), musculoskeletal disorders (2.0 *vs.* 1.5) and hematopoietic cytopenia (2.0 *vs.* 1.4). Furthermore, safety signals identified only for CQ included signals for reported psychotic disorders (ROR 2.8), suicide and self-injury (ROR 4.2) peripheral neuropathy (ROR 3.3), convulsions (ROR 2.6) and decreased appetite (ROR 1.9). Safety signals identified only for HCQ included signals for reported hypersensitivity and gastrointestinal symptoms, nevertheless these RORs were relatively low (1.9 and 1.4 respectively) (Table III and Figure 2).

Lastly, we investigated the association between CQ and HCQ and death using a final sample of 10,279 reports (Figure 3) of which 537 (5.2%) mentioned the use of CQ and9742 (94.8%) the

**Table II.** Disproportionality analysis of chloroquine and hydroxychloroquine.

| | Chloroquine | | | | Hydroxychloroquine | | | |
|---|---|---|---|---|---|---|---|---|
| | N | ROR | LB_ROR | UP_ROR | N | ROR | LB_ROR | UP_ROR |
| Cardiomyopathy | 53 | 22.2 | 16.8 | 29.3 | 222 | 3.2 | 2.8 | 3.7 |
| Retinal disorder | 53 | 12.6 | 9.6 | 16.7 | 493 | 4.2 | 3.8 | 4.6 |
| Corneal disorders | 7 | 8.7 | 4.1 | 18.3 | 39 | 1.8 | 1.3 | 2.4 |
| Cardiac arrythmias | 98 | 7.6 | 6.1 | 9.3 | 465 | 1.2 | 1.1 | 1.3 |
| Severe cutaneous reactions | 15 | 2.9 | 1.8 | 4.9 | 343 | 2.5 | 2.2 | 2.7 |
| Decreased appetite | 17 | 1.9 | 1.2 | 3.1 | 254 | 1.0 | 0.9 | 1.2 |
| Psychotic disorders | 22 | 2.8 | 1.8 | 4.2 | 82 | 0.4 | 0.3 | 0.5 |
| Convulsions | 33 | 2.6 | 1.8 | 3.7 | 200 | 0.6 | 0.5 | 0.6 |
| Headache | 45 | 1.7 | 1.3 | 2.3 | 1071 | 1.5 | 1.4 | 1.5 |
| Hypoglycaemia | 4 | 0.8 | 0.3 | 2.1 | 94 | 0.7 | 0.5 | 0.8 |
| Extrapyramidal symptoms | 5 | 0.6 | 0.2 | 1.4 | 64 | 0.3 | 0.2 | 0.4 |
| Hearing and vestibular disorders | 20 | 2.4 | 1.5 | 3.7 | 302 | 1.3 | 1.2 | 1.5 |
| Peripheral neuropathy | 21 | 3.3 | 2.1 | 5.0 | 186 | 1.0 | 0.9 | 1.2 |
| Suicide and self-injury | 28 | 4.2 | 3.3 | 5.4 | 540 | 0.5 | 0.4 | 0.6 |
| Hepatic disorders | 75 | 3.1 | 2.5 | 4.0 | 1193 | 1.8 | 1.7 | 1.9 |
| Depression | 20 | 1.2 | 0.8 | 1.9 | 285 | 0.6 | 0.6 | 0.7 |
| Gastrointestinal symptoms | 96 | 1.2 | 0.9 | 1.4 | 3027 | 1.4 | 1.3 | 1.4 |
| Hypersensitivity | 85 | 1.2 | 1.0 | 1.5 | 3587 | 1.9 | 1.9 | 2.0 |
| Haematopoieticcytopenia | 45 | 2.0 | 1.5 | 2.7 | 899 | 1.4 | 1.3 | 1.5 |
| Musculoskeletal disorders | 32 | 2.0 | 1.4 | 2.9 | 659 | 1.5 | 1.4 | 1.6 |
| Lactose intolerance | 0 | 0.0 | 0.0 | 0.0 | 1 | 0.4 | 0.1 | 2.7 |

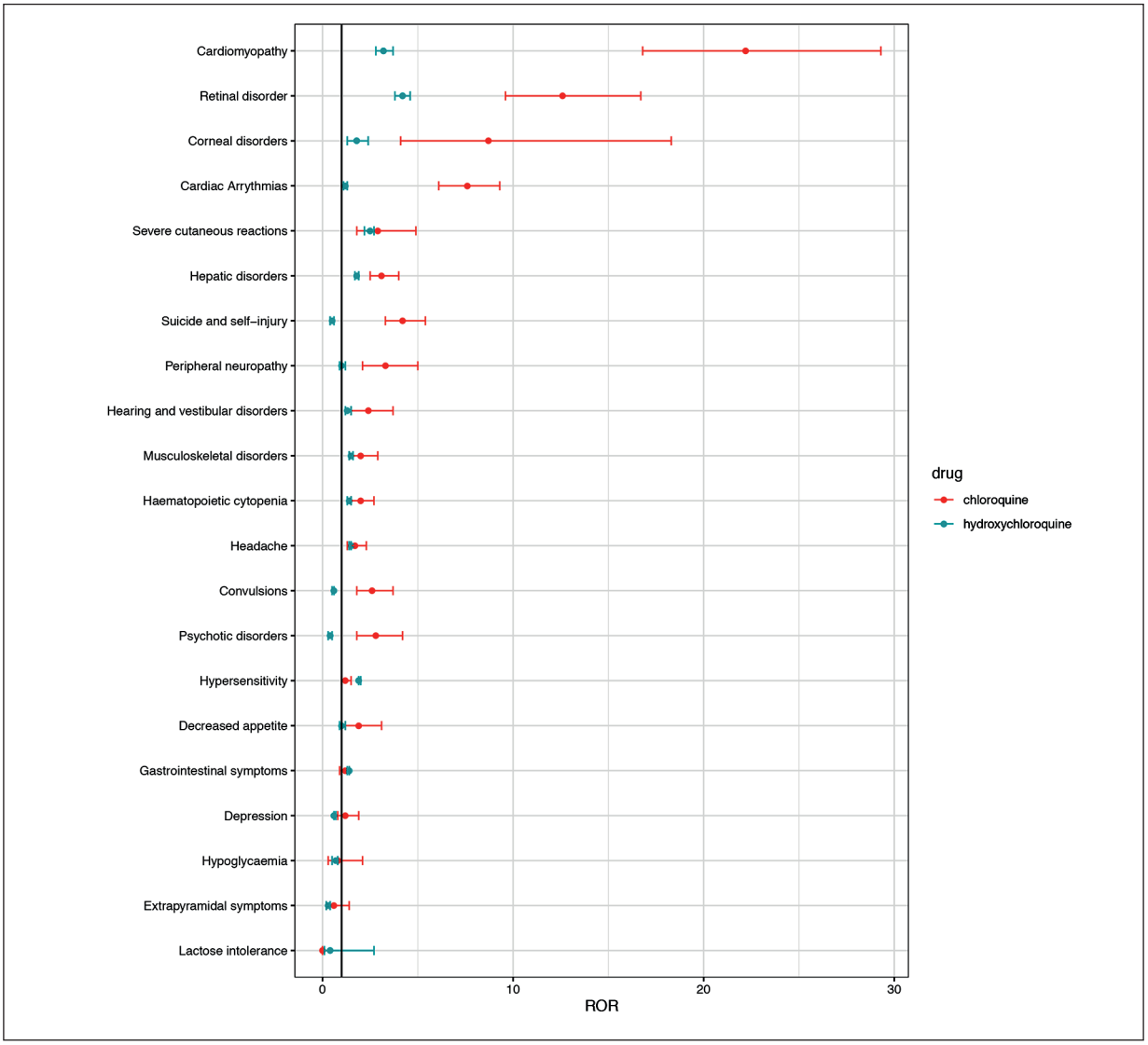


**Figure 1.** Disproportionality analysis of chloroquine and hydroxychloroquine.

use of HCQ. Death was reported in 755 (7.3%) of these reports. In multivariable logistic regression, death was associated with CQ use, advanced age, male sex, patients originating from the United States, with co-reported suicide and self-injury, cardiomyopathy, cardiac arrhythmias, and decreased appetite.

## Discussion

CQ and HCQ exert several pharmacological in vitro effects and have been proposed as repurposed medications in the treatment of COVID-19. They exhibit anti-inflammatory and immunomodulatory properties and concentrate in acidic cytoplasmic vesicles, increasing their pH and leading to dysfunction of several enzymes[17]. Further, it has been proposed that CQ and HCQ interfere with the process of terminal glycosylation of the cellular receptor angiotensin converting enzyme 2, that interacts with the SARS-CoV-2 spike protein and mediates viral entry[18].

According to the drugs summary of product characteristics, very common side effects of both drugs include abdominal pain and nausea, and common side effects include anorexia, diarrhea, vomiting, headache, skin rash, pruritus, and blurred vision (impaired accommodation). The FAERS database usually includes more

**Table III.** Multivariable logistic regression for reporting outcome death of chloroquine and hydroxychloroquine.

| Factor | OR | LB_OR | UP_OR | *p*-value |
|---|---|---|---|---|
| Suicide and self-injury | 8.37 | 6 | 11.7 | 0 |
| Cardiomyopathy | 3.05 | 2.13 | 4.4 | 0 |
| Cardiac arrhythmias | 1.68 | 1.23 | 2.3 | 0 |
| Decreased appetite | 2.3 | 1.2 | 4.4 | 0.01 |
| Gender (Male) | 1.43 | 1.19 | 1.7 | 0 |
| Reporting country (US) | 1.26 | 1.05 | 1.5 | 0.01 |
| Age in report | 1.02 | 1.01 | 1.02 | 0 |
| Hypoglycaemia | 4.85 | 0.96 | 24.5 | 0.06 |
| Date of the report | 0.95 | 0.93 | 0.98 | 0 |
| Hepatic disorders | 1.06 | 0.78 | 1.4 | 0.72 |
| Severe cutaneous reactions | 1.31 | 0.72 | 2.4 | 0.37 |
| Systematic lupusery thematosus | 0.88 | 0.69 | 1.1 | 0.27 |
| Haematopoieticcytopenia | 0.95 | 0.67 | 1.3 | 0.76 |
| Hypersensitivity | 0.67 | 0.5 | 0.9 | 0.01 |
| Gastrointestinal symptoms | 0.66 | 0.49 | 0.9 | 0.01 |
| Musculoskeletal disorders | 0.78 | 0.47 | 1.3 | 0.34 |
| Drug (HCQ) | 0.6 | 0.44 | 0.8 | 0 |
| Drug (CQ) | 1.7 | 1.3 | 2.3 | 0 |
| Arthritis | 0.45 | 0.38 | 0.5 | 0 |
| Malaria | 0.74 | 0.31 | 1.8 | 0.5 |
| Corneal disorders | 1.37 | 0.3 | 6.2 | 0.68 |
| Headache | 0.42 | 0.22 | 0.8 | 0.01 |
| Depression | 0.42 | 0.19 | 0.9 | 0.02 |
| Peripheral neuropathy | 0.37 | 0.13 | 1 | 0.06 |
| Convulsions | 0.44 | 0.09 | 2.2 | 0.31 |
| Psychotic disorders | 0.07 | 0.01 | 0.5 | 0.01 |
| Retinal disorders | 0.03 | 0 | 0.2 | 0 |
| Hearing and vestibular disorders | 0 | 0 | INF | 0.94 |
| Extrapyramidal symptoms | 0 | 0 | INF | 0.98 |

severe side effects, while the mildest ones are underreported. However, some of the common events were captured in our analysis as safety signals (decreased appetite, gastrointestinal symptoms, hypersensitivity, severe cutaneous reactions, headache). Interestingly, musculoskeletal disorders (including muscle atrophy, weakness, and pain, and neuromyopathy) and peripheral neuropathy also demonstrated RORs indicative of safety signals, especially with the use of CQ.

The strongest safety signals found in our analysis were for reported cardiomyopathy, retinal disorders, corneal disorders, and arrhythmias. Notably, the ROR values for these adverse events were significantly higher for CQ than HCQ, especially for cardiomyopathy (22.2 *vs.* 3.2). The higher cardiac risk of CQ was further supported by the increased risk of arrhythmias (ROR 7.6). Cardiomyopathy and heart rhythm problems are well recognized adverse events of CQ analogues, especially in combination with azithromycin and other QT prolonging medications[19,20]. These findings are congruent with a recently published disproportionality analysis focusing on cardiovascular adverse events associated with CQ and HCQ that suggested higher reporting rates of cardiomyopathy, QT prolongation, rhythm disorders, and heart failure which were also associated with higher rates of severe outcomes[21].

Central and peripheral nervous system disorders including convulsions (ROR 2.6) and peripheral neuropathy (ROR 3.3) were also identified only for CQ and interestingly, a safety signal for psychosis (ROR 2.8) was also revealed. Many case reports and epidemiological studies have previously linked the use of CQ analogues (especially CQ and mefloquine) to an increased risk of neuropsychiatric adverse effects, such as depression or psychoses[22], while acute psychotic behavior was associated with CQ decades ago[23]. A recently published disproportionality analysis of the FAERS focusing on the neuropsychiatric adverse events of CQ reported a significant, yet marginal (aRORs between 1.3-2.1) association between the use of CQ and the reporting of amnesia, delirium, hallucinations, loss of consciousness, and depression, while a potential

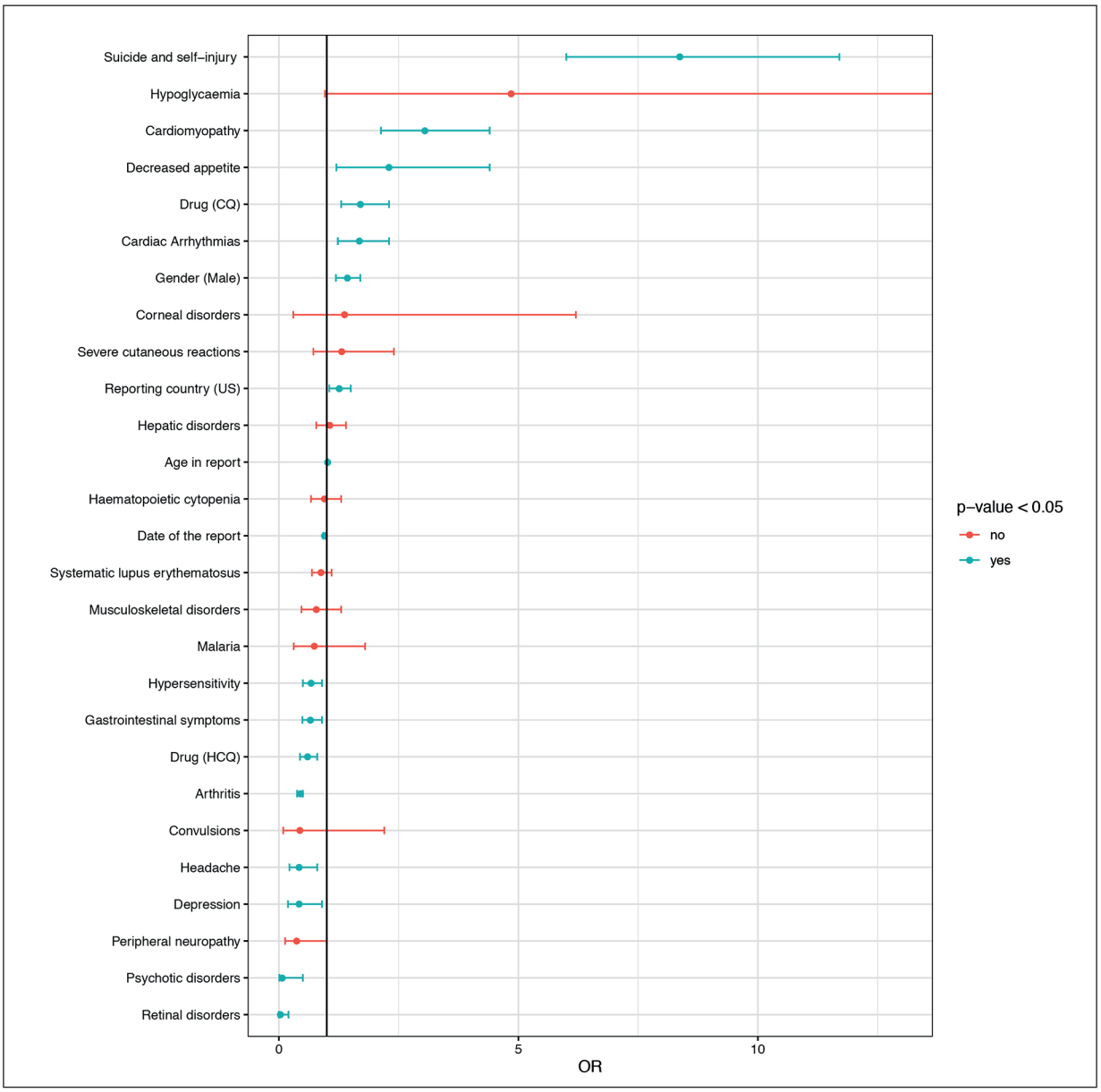


**Figure 2.** Multivariable logistic regression for reporting outcome death of chloroquine and hydroxychloroquine.

link with an increased risk of suicide or psychosis was not detected. However, this analysis had several methodological limitations and included a limited time period of FAERS data (Q42012-Q42019)[24].

One of our findings that raises concerns is the signal for reported suicide and self-injury (ROR 4,19) for CQ. Death due to CQ overdose has been previously reported, even during its first years of use. In 1964 a report of 13 fatalities was published and suicide was the most likely cause of death in all cases. This 'milestone' publication highlighted the rapid time course of events following overdose, since CQ is rapidly absorbed from the gastrointestinal tract, the onset of symptoms is fast, and death occurs in less than two hours[23]. Voluntary intoxication with CQ is a major medical and social problem especially in developing countries. A study of 884 cases in Mali revealed that self-poisoning was most commonly associated with suicide attempts and self-induced abortion and in the majority of them CQ was used[25]. CQ is a common agent used in suicide attempts and there is extensive

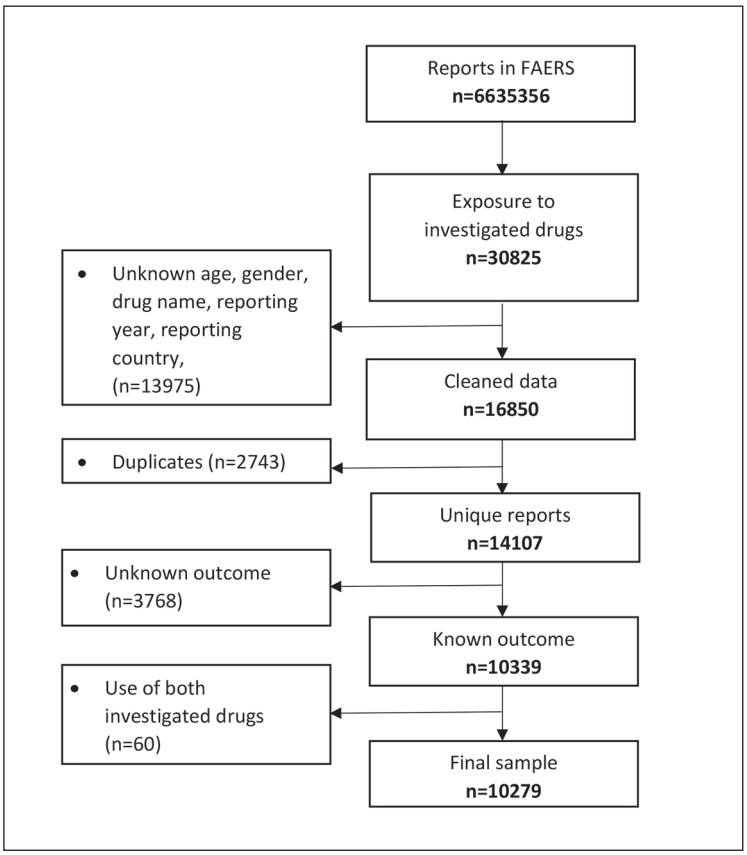


**Figure 3.** Flow chart of chloroquine and hydroxychloroquine reports for the analysis of reporting outcome death.

experience regarding its toxicity. Based on previous studies, CQ is 2 to 3 times more toxic than HCQ and has a narrow therapeutic index[26]. CQ overdose causes severe and rapid symptomatology, with symptoms frequently observed within 30 minutes. Death usually occurs within one to three hours after ingestion and the main cause of death is cardiac arrest[27]. On the other hand, HCQ overdose is rarely reported in the literature and there is limited experience to characterize a HCQ overdose, while lethal dose or toxic dose cut-off are not established[28]. Our multivariable logistic regression analysis revealed that reports including the outcome of death were more frequently associated with CQ use and co-reported suicide and self-injury. Death was also significantly associated with cardiomyopathy and cardiac arrhythmias, which are well-known complications of CQ/HCQ treatment in COVID-19 patients as well.

The present study has certain limitations. Pharmacovigilance databases like FAERS suffer from under-reporting, temporal patterns of reporting, notoriety of the adverse event and suboptimal quality of reports[14]. Further, disproportionality analysis is a statistical method that cannot provide clinical causality assessment; thus, any identified association does not imply causation. Additionally, it is important to notice that 'death' may be reported as an adverse event (preferred term) or as an outcome (i.e., the final clinical event resulting from the adverse event). In the latter scenario, causality is even more challenging, because it is unfeasible to attribute death to the use of any drug, especially considering the complexity and diversity of patients. However, we deliberately focused our analyses on death as an outcome and performed a multivariable logistic regression analysis, because death is in general the most important outcome to validate the clinical profile of any drug.

## Conclusions

The major strength of this study is the large number of reports, and the comprehensive list of adverse events. Our results confirm previously published evidence[29] and suggest that HCQ may have a safer clinical profile compared to CQ.

### Conflict of Interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

### Ethics Approval and Consent to Participate
The analysis used data from FAERS, which is a public anonymized database and ethical approval is not applicable.

### Availability of Data and Materials
Data that support the findings of the disproportionality analysis are not available since the analysis was conducted within OpenVigil 2.1-MedDRA. The data and R code that support the findings of the analysis of reported mortality are available from the corresponding author upon request.

### Authors' Contribution
G.P. study design, literature search, data interpretation, manuscript drafting and editing, S.S. study design, data collection, analysis, interpretation, D.C. data collection and analysis, manuscript drafting, D.G. literature search, manuscript editing, E.S. literature search, manuscript editing, D.T. literature search, manuscript editing and T.E. data interpretation, manuscript editing.

## References


1) WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, Alejandria MM, Hernández García C, Kieny MP, Malekzadeh R, Murthy S, Reddy KS, Roses Periago M, Abi Hanna P, Ader F, Al-Bader AM, Alhasawi A, Allum E, Alotaibi A, Alvarez-Moreno CA, Appadoo S, Asiri A, Aukrust P, Barratt-Due A, Bellani S, Branca M, Cappel-Porter HBC, Cerrato N, Chow TS, Como N, Eustace J, García PJ, Godbole S, Gotuzzo E, Griskevicius L, Hamra R, Hassan M, Hassany M, Hutton D, Irmansyah I, Jancoriene L, Kirwan J, Kumar S, Lennon P, Lopardo G, Lydon P, Magrini N, Maguire T, Manevska S, Manuel O, McGinty S, Medina MT, Mesa Rubio ML, Miranda-Montoya MC, Nel J, Nunes EP, Perola M, Portolés A, Rasmin MR, Raza A, Rees H, Reges PPS, Rogers CA, Salami K, Salvadori MI, Sinani N, Sterne JAC, Stevanovikj M, Tacconelli E, Tikkinen KAO, Trelle S, Zaid H, Røttingen JA, Swaminathan S. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2021; 11; 384: 497-511.
2) Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, Mourão MPG, Brito-Sousa JD, Baía-da-Silva D, Guerra MVF, Hajjar LA, Pinto RC, Balieiro AAS, Pacheco AGF, Santos JDO Jr, Naveca FG, Xavier MS, Siqueira AM, Schwarzbold A, Croda J, Nogueira ML, Romero GAS, Bassat Q, Fontes CJ, Albuquerque BC, Daniel-Ribeiro CT, Monteiro WM, Lacerda MVG; CloroCovid-19 Team. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. JAMA Netw Open 2020; 24; 3: e208857.
3) U.S. Food & Drug Administration. FDA Drug Safety Communication: FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. Published 2020. Accessed May 3, 2020. www.clinicaltrials.gov
4) Rajasingham R, Bangdiwala AS, Nicol MR, Skipper CP, Pastick KA, Axelrod ML, Pullen MF, Nascene AA, Williams DA, Engen NW, Okafor EC, Rini BI, Mayer IA, McDonald EG, Lee TC, Li P, MacKenzie LJ, Balko JM, Dunlop SJ, Hullsiek KH, Boulware DR, Lofgren SM; COVID PREP team. Hydroxychloroquine as Pre-exposure Prophylaxis for Coronavirus Disease 2019 (COVID-19) in Healthcare Workers: A Randomized Trial. Clin Infect Dis 2021; 1; 72: e835-e843.
5) Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, Skipper CP, Nascene AA, Nicol MR, Abassi M, Engen NW, Cheng MP, LaBar D, Lother SA, MacKenzie LJ, Drobot G, Marten N, Zarychanski R, Kelly LE, Schwartz IS, McDonald EG, Rajasingham R, Lee TC, Hullsiek KH. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. N Engl J Med 2020; 6; 383: 517-525.
6) Chowdhury MS, Rathod J, Gernsheimer J. A Rapid Systematic Review of Clinical Trials Utilizing Chloroquine and Hydroxychloroquine as a Treatment for COVID-19. Acad Emerg Med 2020; 27: 493-504.
7) Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, Wu Y, Xiao W, Liu S, Chen E, Chen W, Wang X, Yang J, Lin J, Zhao Q, Yan Y, Xie Z, Li D, Yang Y, Liu L, Qu J, Ning G, Shi G, Xie Q. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020; 14; 369: m1849.
8) Group TRC. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med 2020; 383: 2030-2040.
9) Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM, Williams DA, Okafor EC, Pullen MF, Nicol MR, Nascene AA, Hullsiek KH, Cheng MP, Luke D, Lother SA, MacKenzie LJ, Drobot G, Kelly LE, Schwartz IS, Zarychanski R, McDonald EG, Lee TC, Rajasingham R, Boulware DR. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19: A Randomized Trial. Ann Intern Med 2020; 20; 173: 623-631.
10) Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, Damiani LP, Marcadenti A, Kawano-Dourado L, Lisboa T, Junqueira DLM, de Barros E Silva PGM, Tramujas L, Abreu-Silva EO, Laranjeira LN, Soares AT,

Echenique LS, Pereira AJ, Freitas FGR, Gebara OCE, Dantas VCS, Furtado RHM, Milan EP, Golin NA, Cardoso FF, Maia IS, Hoffmann Filho CR, Kormann APM, Amazonas RB, Bocchi de Oliveira MF, Serpa-Neto A, Falavigna M, Lopes RD, Machado FR, Berwanger O; Coalition Covid-19 Brazil I Investigators. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med 2020; 19; 383: 2041-2052.

11) Abd-Elsalam S, Esmail ES, Khalaf M, Abdo EF, Medhat MA, El Ghafar MSA, Ahmed OA, Soliman S, Serangawy GN, Alboraie M. Hydroxychloroquine in the treatment of COVID-19: A multicenter randomized controlled study. Am J Trop Med Hyg 2020; 103:1635-1639.

12) Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, Cani DS, Cerini M, Farina D, Gavazzi E, Maroldi R, Adamo M, Ammirati E, Sinagra G, Lombardi CM, Metra M. Cardiac Involvement in a Patient with Coronavirus Disease 2019 (COVID-19). JAMA Cardiol 2020; 5: 819-824.

13) Van den Broek MPH, Möhlmann JE, Abeln BGS, Liebregts M, van Dijk VF, van de Garde EMW. Chloroquine-induced QTc prolongation in COVID-19 patients. Netherlands Hear J 2020; 28: 406-409.

14) Sakaeda T, Tamon A, Kadoyama K, Okuno Y. Data mining of the public version of the FDA adverse event reporting system. Int J Med Sci 2013; 10: 796-803.

15) Cepaityte D, Siafis S, Papazisis G. Safety of antipsychotic drugs: A systematic review of disproportionality analysis studies. Behav Brain Res 2021; 404.

16) Van Puijenbroek EP, Bate A, Leufkens HGM, Lindquist M, Orre R, Egberts ACG. A comparison of measures of disproportionality for signal detection is spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf 2002; 11: 3-10.

17) Al-Bari AA. Chloroquine analogues in drug discovery: New directions of uses, mechanisms of actions and toxic manifestations from malaria to multifarious diseases. J Antimicrob Chemother 2014; 70: 1608-1621.

18) Freund NT, Roitburd-Berman A, Sui J, Marasco WA, Gershoni JM. Reconstitution of the receptor-binding motif of the SARS coronavirus. Protein Eng Des Sel 2015; 28: 567-575.

19) Administration USF and D. Emergency Use Authorization - Impella RP. Published 2020. Accessed April 5, 2020. https://www.fda.gov/media/138460/download

20) Borba M, de Almeida Val F, Sampaio VS, Alexandre MA, Melo GC, Brito M, Mourao M, Sousa JD, Guerra MV, Hajjar L, Pinto RC. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb cl. medRxiv 2020

21) Goldman A, Bomze D, Dankner R, Hod H, Meirson T, Boursi B, Maor E. Cardiovascular adverse events associated with hydroxychloroquine and chloroquine: A comprehensive pharmacovigilance analysis of pre-COVID-19 reports. Br J Clin Pharmacol 2021; 87: 1432-1442.

22) Meier CR, Wilcock K, Jick SS. The Risk of Severe Depression, Psychosis or Panic Attacks with Prophylactic Antimalarials. Drug Saf 2004; 27: 203-213.

23) Kiel FW. Chloroquine Suicide. JAMA J Am Med Assoc 1964; 190: 398-400.

24) Sato K, Mano T, Iwata A, Toda T. Neuropsychiatric adverse events of chloroquine: A real-world pharmacovigilance study using the FDA adverse event reporting system (FAERS) database. Biosci Trends 2020; 14: 139-143.

25) Diallo T, Hami H, Maiga A, Coulibaly B, Maiga D, Mokhtari A, Soulaymani R, Soulaymani A. [Epidemiology and risk factors for voluntary intoxication in Mali]. Sante Publique 2013; 25: 359-366.

26) Jordan P, Brookes JG, Nikolic G, Le Couteur DG. Hydroxychloroquine overdose: Toxicokinetics and management. J Toxicol Clin Toxicol 1999; 37: 861-864.

27) Clemessy JL, Borron SW, Baud FJ, Favier C, Hantson PE, Vicaut E. Hypokalaemia related to acute chloroquine ingestion. Lancet 1995; 346: 877-880.

28) Marquardt K, Albertson TE. Treatment of hydroxychloroquine overdose. Am J Emerg Med 2001; 19: 420-424.

29) Zhou D, Dai SM, Tong Q. COVID-19: A recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. J Antimicrob Chemother 2020; 75: 1667-1670.