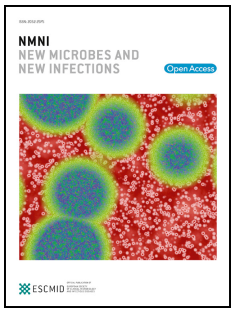


# Clinical Efficacy of Chloroquine derivatives in COVID-19 Infection: Comparative meta-analysis between the Big data and the real world

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PII: S2052-2975(20)30061-5

DOI: https://doi.org/10.1016/j.nmni.2020.100709

Reference: NMNI 100709

To appear in: *New Microbes and New Infections*

Received Date: 8 May 2020

Revised Date: 28 May 2020

Accepted Date: 4 June 2020

Please cite this article as: Million M, Gautret P, Colson P, Roussel Y, Dubourg G, Chabriere E, Honore S, Rolain J-M, Fenollar F, Fournier P-E, Lagier J-C, Parola P, Brouqui P, Raoult D, Clinical Efficacy of Chloroquine derivatives in COVID-19 Infection: Comparative meta-analysis between the Big data and the real world, *New Microbes and New Infections*, https://doi.org/10.1016/j.nmni.2020.100709.

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# Clinical Efficacy of Chloroquine Derivatives in COVID-19 Infection: Comparative Meta-analysis between the Big Data and the Real World

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**Running title**: Efficacy of Chloroquine derivatives for COVID-19 in the real world

**Keywords**: coronavirus, COVID-19, SARS-CoV-2, Hydroxychloroquine, Chloroquine, meta-analysis

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# Clinical Efficacy of Chloroquine Derivatives in COVID-19 Infection: Comparative Meta-analysis between the Big Data and the Real World

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**Keywords**: coronavirus, COVID-19, SARS-CoV-2, Hydroxychloroquine, Chloroquine, meta-analysis, mortality, Big data, Medical world

**Abstract**

In the context of the current COVID-19 pandemic, we conducted a meta-analysis on the effects of chloroquine derivatives in patients, based on unpublished and published reports available publicly on the internet as of May, 27, 2020. The keywords “hydroxychloroquine”, “chloroquine”, “coronavirus”, “COVID-19” and “SARS-Cov-2” were used in the PubMed, Google Scholar and Google search engines without any restrictions as to date or language. Twenty studies were identified involving 105,040 patients (19,270 treated patients) from nine countries (Brazil, China, France, Iran, Saudi Arabia, South Korea, Spain, and USA). Big data observational studies were associated with conflict of interest, lack of treatment dosage and duration, and absence of favorable outcome. Clinical studies were associated with favorable outcomes and details on therapy. Among clinical studies, three of four randomized controlled trials reported a significant favorable effect. Among clinical studies, a significant favorable summary effect was observed for duration of cough (Odds ratio (OR), 0.19, p = .00003), duration of fever (0.11, p = .039), clinical cure (0.21, p = .0495), death (0.32, p = $4.1x10^{-6}$) and viral shedding (0.43, p = .031). A trend for a favorable effect was noted for the outcome “death and/or ICU transfer” (0.29, p = .069) with a point estimate remarkably similar to that observed for death (~0.3). In conclusion, a meta-analysis of publicly available clinical reports demonstrates that chloroquine derivatives are effective to improve clinical and virological outcomes but, more importantly, it reduces mortality by a factor 3 in patients infected with COVID-19. Big data are lacking basic treatment definitions and are linked to conflict of interest.

## Introduction

In periods of large epidemics such as the current COVID-19 pandemic, information spread very fast with different levels of reliability including fake-news, press releases, pre-prints and peer-reviewed published reports. In addition, it seems that there is a competition between low-cost generic medications that are potentially effective against SARS-CoV-2 and very expensive new drugs that are not yet approved, implying financial and organizational issues, stakeholders expectations, and administrative/policy complexity. This may lead to positions that are not only driven by science and public health.

In this context, we aimed to conduct a meta-analysis on the effects of chloroquine derivatives (i.e. hydroxychloroquine (HCQ) or chloroquine (CQ)) in COVID-19 patients, based on all available information from pre-prints and peer-reviewed published reports. For pre-prints, we asked two reviewers of our team to provide an open review of the content (Supplementary data) and we considered the comment of an external scientist (1). We were surprised to find major discrepancies between study conclusions ranging from dramatic clinical improvement to dramatic increase in mortality rates under chloroquine derivative treatment. We sought to understand what could explain such differences. We recently discussed the fact that it does not make sense to investigate a summary effect when inconsistent studies and unexplained heterogeneity makes the average effect difficult to interpret and potentially misleading (2). Thus, we first investigated the differential characteristics of studies showing a very favorable effect of the treatment and of those showing a clearly deleterious effect.

First, we found that a clear standardized protocol for treatment (3) and follow-up was detailed in studies conducted by clinicians (clinical studies), whereas it was completely lacking in studies conducted by public health experts on a large number of patients whose

data were extracted from electronic medical records (big data). We have already pointed out the limitations of these "big data" analyses in relation with clinical inaccuracy (4).

Adequate timing (early versus delayed administration), dosage, screening of contraindications, adjuvant measures and monitoring following standardized protocols are critical in the benefit risk ratio of any drug against infectious diseases (3). Based on our 30-years' experience of treating hundreds of patients suffering Q fever endocarditis and Whipple's disease with HCQ 600 mg/day (200 mg *tid*) (5,6), we know that this drug is effective with negligible side effects when compared to the fatal outcome of both diseases. Chloroquine derivatives (and paracetamol) can be used to commit suicide with overdose (7) and may be fatal, at therapeutic dosage, when contraindications and adjuvant measures are not carefully followed. In this context, it is expected that studies using double dose HCQ (1200 mg/day) in COVID-19 would be associated with toxicity (8). Accordingly, we investigated whether a well described treatment protocol, including dosage, for at least 48 hours was associated with outcome.

From our seminal study (9), we observed an improved efficacy of the combination of HCQ and azithromycin (AZ) when compared to HCQ alone. A synergistic effect was confirmed by *in vitro* studies (10). This led us to change our standardized protocol by shifting from a mono-therapy to a combined therapy. This combination could not be neglected in the treatment of COVID-19 and was therefore also analyzed in the present study.

In the context of a pandemic with an unknown virus, development of new drugs is a major opportunity for "big pharma" industry, and this is potentially associated with a very high risk of conflicts of interest. This led us to consider these conflicts of interest as a moderator variable in the present work. As major financial issues are at stake, and may impact the interpretation of scientific data, we felt it was important to mention that none of us have conflict of interest with any pharmaceutical company.

We performed this meta-analysis taking into account three important moderator variables: clinical studies or studies based on electronic registry data analysis (big data), studies based on a mono-therapy (chloroquine derivatives) or a combined therapy (HCQ-AZ), and finally studies where authors had potential conflicts of interest and study where authors had no conflicts of interest. In the context of the current pandemic, providing a timely and critical analysis of available data on this topic seems appropriate to us, in a public health perspective.

**Methods**

We conducted a meta-analysis of studies evaluating the effects of chloroquine derivatives against SARS-CoV-2 in groups of COVID-19 patients as compared to control groups of patients who did not receive chloroquine derivatives. In these studies, groups were expected to be similar with respect to demographics, chronic conditions, clinical presentation at enrolment and use of other antiviral drugs during the course of the disease. The keywords “hydroxychloroquine”, “chloroquine”, “coronavirus”, “COVID-19” and “SARS-Cov-2” were used in the PubMed, Google Scholar and Google search engines without any restrictions as to date or language. Preprints were also included. Open reviews and reviewer’s recommendations regarding preprints are available in the supplementary data. Articles published in peer-reviewed journals, pre-prints and articles available on the internet, even when not published on official websites, were included.

The following outcomes were considered: hospitalization rate, duration of cough, duration of fever, clinical cure, lymphocyte count, C-reactive protein level, Interleukin-6 level, thoracic CT-scan imaging, aggravation to severe, death, transfer to intensive care unit (ICU), ventilation, length of hospital stay and persistent viral shedding as assessed by PCR.

Only studies comparing a group of COVID19 patients treated with a chloroquine derivative to a control group without chloroquine derivatives were included. Non-comparative (single arm) studies and studies comparing two groups treated with chloroquine derivatives at different dosages or with different delay of treatment were excluded.

Studies were classified as "big data" studies when conducted on electronic medical records extracted by public health specialists and epidemiologists who did not care COVID-19 patients themselves. Conversely, studies were classified as "clinical studies" when mentioning details of treatments (dosages, duration, contraindications, monitoring…) and conducted by authors physicians (infectious diseases and internal medicine specialists, and pulmonologists) who cared COVID-19 patients themselves. Conflicts of interest were retrieved from author statements in the article. Another check was performed using Euros for Docs (https://www.eurosfordocs.fr/) and Dollars for Docs (https://projects.propublica.org/docdollars/) websites. We considered that there was a conflict of interest when funding by the pharmaceutical industry exceeds 50,000€, over seven years.

Studies were classified as "Pro", when at least one comparison reported a significant improvement, and none were associated with a significant deleterious effect in the treated group. Studies were classified as "Cons" when none of the comparisons reported a significant favorable outcome and/or at least one comparison report a significant deleterious outcome.

The meta-analysis was performed with a randomized model using Comprehensive Meta-Analysis v3 (Biostat, Englewood, NJ, USA) as recommended by Borenstein *et al.* (11). This software made it possible to include dichotomous outcomes (number of events out of the total) and quantitative outcomes (mean in each group, sample size, p-value). Heterogeneity was considered substantial when $I^2 > 50\%$. A p-value $< 0.05$ was considered significant. A heat map analysis was performed to test a possible clustering between Pro and Cons studies, clinical and big data study design, well described treatment protocol and not described

125 treatment protocol, and conflict of interest and no conflict of interest, using XLSTAT

126 v2020.2.2 (Addinsoft, Paris, France).

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**Results**

Twenty-three comparative studies were screened. Three studies were excluded because they compared two groups treated with a chloroquine derivative (delayed initiation of treatment (12), high versus low dose (8), combination therapy with or without zinc (13)). As a result, twenty studies were identified involving 105,040 patients (19,270 patients treated with a chloroquine derivatives including 11,247 in combination with a macrolide) from nine countries (Brazil, China, France, Iran, Saudi Arabia, South Korea, Spain, and USA) (Table S1). The 20 studies included 8 published papers, 9 pre-prints published on MedRxiv, 1 pre-print published on preprints.org, and 2 available on the internet (uniform resource locator (url) provided in Table S2). All but 2 papers in Chinese (14) and French (15) were written in English. The Chinese study (14) was translated and included.

We noted that registry studies based on electronic medical records did not mentioned the dosage or included several dosages of the chloroquine derivatives used (16-20). We found that in several studies, patients used several molecules with established or potential antiviral properties. For instance, in China and Iran, almost all patients used multiple antivirals: lopinavir/ritonavir, oseltamivir, entecavir, ribavirin, umifenovir and nebulisation of interferon aerosol. In eight studies (15,18-24) patients used the combined therapy that we have recommended (HCQ and AZ combination (9)). Four RCTs were included in this analysis (14,25-27).

We observed major methodological pitfalls in some studies. Lymphopenia, a marker of severity (28), was significantly more frequent in the treated group in one study (17). In another study, 8 patients received HCQ in the “untreated” group (29). In this study, none of the 15 patients treated with combined therapy (HCQ + azithromycin) died or were transferred to the ICU, and the difference was significant with the untreated control group. Strikingly, this was not analyzed because it was not prespecified in the study protocol. In another work (27),

all results reporting a favorable effect of HCQ in the first version of the preprint (30) on alleviation of symptoms and C-reactive protein were removed in the final preprint version (27) and in the published version of the article (31). Finally, the largest study that has been done (18), is impossible to analyze because there is no notification of hospital sources or referral to any physician. It is not known if the authors of this study saw a single patient infected with COVID-19.

**Big data and clinical studies were perfectly discriminated by unsupervised clustering**

As we observed that several studies reported a clear favorable effect (15, 21-23, 25, 26, 30, 32-35) but others reported no (14,16,17,19,24,29) or a clear deleterious effect (18), we primarily performed a unsupervised clustering analysis including the following variables : "Pro" / "Cons" studies, "big data" versus "clinical studies", "detailed" or "absence of detailed treatment", presence or absence of a conflict of interest (Figure 1).

In this unsupervised analysis, only the variable "big data" versus "clinical" studies yielded to a perfect clustering. All other variables (conflict of interest, Pro / Cons, detailed treatment) did not provide a perfect clustering. We subsequently investigate whether each of these parameters was significantly associated to favorable or unfavorable effect.

All "big data" studies reported a lack of beneficial effect of the treatment and were significantly more likely associated with "Cons" variable (5/5 vs 3/15, $p = .004$). This was also observed by examination of the meta-analysis forest plot (Figure 2, Table S3 to S8). In addition, both "conflicts of interest" ($p = .01$) and "not described treatment protocol" variables ($p = .004$) were associated with "Cons" variable. Conversely, clinical studies were more likely to report a favorable effect of chloroquine derivatives in COVID-19 patients ($p < .05$). Consistently, clinical studies with detailed treatment protocol were more likely associated with the observation of a favorable effect of the treatment ($p < .05$).

**Conflict of interests are linked to a part of the biases in favor of Cons**

We found 4 studies with author conflicts of interest (Figure 1, Table S1). ”Conflicts of interest” variable was associated with big data studies (3/5 vs 1/15, $p < .05$) and with a negative direction of treatment effect ($p < 0.05$, Figure 1).

**The direct care or patients (clinical versus big data) explains the direction of effect**

We primarily tested if the studies involving direct care of patients (clinical studies performed by physician who took care of patients) were associated with a different direction of effect compared to “big data” studies (Figure 2). The visual examination of the forest plot clearly evidenced that “big data” studies reported no (16,17,19,20) or deleterious effect (18). In contrast, several clinical studies reported significant favorable effects notably regarding hospitalization rate (21), duration of fever (25,33), duration of cough (23,25), clinical cure (15,30), C-reactive protein levels (30), interleukin-6 levels (35), thoracic CT-imaging (25), length of hospital stay (23,26), death or ICU transfer (22,32), death (34,35) and persistent viral shedding (9,23,33).

We compared the proportion of comparisons reporting significant differences according to treatment. In the big data analyses, 4 comparisons reported a significant effect, and all were deleterious (4/4). In the clinical studies, 17 comparisons reported a significant effect, and all were beneficial. The difference was highly significant (4/4 vs 0/17, Bilateral Mid-P exact test, $p = .00016$). This was also supported by the significant heterogeneity between the two subgroups (big data vs. clinical studies, mixed effect analysis, Q-value 51.8, $p < .001$).

**Three of four randomized controlled trials reported a significant favorable effect**

Four RCTs were included (14,25-27,30,31). All were performed in China. Three of them reported significant favorable effects. Chen Z *et al*. (25) reported a significant favorable effect on duration of fever, duration of cough and thoracic CT-scan imaging. Huang reported a significant reduction of length of hospital stay (26). Interestingly, Tang et al. (27) reported in the first version of their preprint (30) a significant favorable effect on alleviation of symptoms (post hoc analysis) and C-reactive protein reduction (subgroup with baseline increased C-reactive protein), but these results were removed in the final published version of the manuscript (27,31). This was requested by editors and reviewers from the British Medical Journal (open review) where the final version was published because this was not prespecified in the study protocol. In addition, they were concerned about the justification of including these secondary outcomes results and post-hoc analysis from under-powered sample size (due to early termination). This is surprising since a lack of power may be associated with a risk of not finding a difference when there is one, but not with a risk of finding a difference when there is none. None of these RCTs reported a significant deleterious effect.

**Effect of chloroquine derivatives without azithromycin**

As several studies addressed the effectiveness of the combination of chloroquine derivatives with a macrolide, specifically AZ, we tested if the favorable clinical effect (observed in clinical studies) remained after exclusion of comparisons with combination therapy (Supplementary Figure 1). A favorable effect was still observed for duration of cough (n = 1, point estimate 0.12, p = .001), duration of fever (n = 2, 0.05, p = .002), clinical cure (n = 2, 0.48, p = .022), C-reactive protein levels (n = 1, 0.55, p = .045), interleukin-6 levels (n = 1, 0.43, p = .002), and death (n= 3, 0.31, p < .001). Interestingly, the effect was not significant anymore for persistent viral shedding (n = 7, 0.51, 0.20-1.33, p = 0.17).

**Outcomes with a significant summary effect in clinical studies**

We found a favorable summary effect on duration of cough (n = 2, point estimate 0.19, 95% confidence interval 0.09-0.42, p = .00003 – $I^2$ = 0%), duration of fever (n = 3, 0.11, 0.01-0.90, p=.039 – $I^2$ = 91%, p < .001), clinical cure (n = 3, 0.21, 0.05-1.0, p = .0495 – $I^2$ = 81%, p < .001), and death (n = 4, 0.32, 0.19-0.52, p = 4.1 x $10^{-6}$ – $I^2$ = 0%, p = .71 – Table S9). A trend for the outcome "death or ICU transfer" was also noted (n = 3, 0.29, 0.08-1.10, p = .069 – $I^2$ = 85%, p < .002) with a point estimate very similar to that observed for the death outcome (0.3, e.g. a 3 fold decrease in the risk of ICU transfer and/or death). For persistent viral shedding, 10 comparisons were included with a significant favorable effect on persistent viral shedding (n = 10, point estimate 0.43, 0.20-0.92, p = .031 – $I^2$ = 75%, p < .001).

**Discussion**

Chloroquine derivatives present a paradox. On one hand, the heterogeneity of patients and treatment schemes make it difficult to obtain a clear picture while the epidemic is still ongoing. On the other hand, despite controversy, only chloroquine derivatives have been used by physicians on a large-scale basis as treatment for COVID-19 (36). According to the Sermo Real Time Covid-19 Barometer (https://www.sermo.com/, consulted 27 May), for over 20,000 physicians across 30 countries, chloroquine derivatives are the first medication used to treat COVID-19 patients in ICUs (43% - except oxygen, anti-clotting / anticoagulants, steroids and norepinephrine) and in other hospital settings (52% - except oxygen), and the second in outpatient settings (33%, after AZ and similar antibiotics).

Indeed, we were challenged by the major discrepancies between the results of the various published studies and our experience at the IHU where 7800 ECGs were performed in 4000 patients. In order to understand which elements could lead to contradictory results, we

compared the results of studies carried out by clinicians (real world) and those carried out by database analysts (virtual world of big data - Figure 1). The clinical studies used a standardized treatment protocol with methods that included assessment of contraindications, daily dosage, adjuvant measures and duration of treatment with at least 48 hours of treatment before the objective could be assessed. For example, assessment of kalemia and electrocardiogram is critical prior to treatment, especially when the chloroquine derivative is combined with AZ (37). At the same time, we observed that virtual big data studies did not mention these elements and considered the presence of chloroquine derivative prescription in electronic records in a binary fashion. Obviously, the number of patients included in the database analyses was much higher than the number of patients included in the clinical studies, because these databases are made up of thousands of electronic medical records (EMR). As mentioned in the past (4), this type of studies have tremendous statistical power but are limited by clinical inaccuracy that makes their conclusions difficult to believe.

As a matter of fact, we cannot believe that in some series there is up to 8% of deaths due to cardiac rhythm disorders (18), whereas all the electrocardiograms performed in the IHU (our center) for 4000 patients and analyzed by a team of cardiologists specializing in rhythmology have not seen any, except for an increase in QTc which justified stopping treatment in only 3 cases (38). Under these conditions we thought that people who really observed the patients had a very different perception of the results from people who had not observed the patients but retained observations. The major elements of this study are that, overall there is an extremely significant difference between the analyses of data not collected directly by the doctors who cared patients and the studies carried out by the physicians who set up these studies and cared patients, including the randomized studies. The second thing is that in these studies conducted electronically, the treatment is never really specified, with the dosage and duration of treatment making it impossible to assess efficacy (dose too low) or

toxicity (dose too high). In addition to this major bias, we also noted a significant bias when the authors had conflicts of interest due to their relationship with industrialists trying to market molecules in the same therapeutic framework competing with HCQ.

For discrepancies in published data, favorable evidence for chloroquine derivatives is sometimes censored by the journal (open review of Tang's randomized controlled trial, published in the British Medical Journal (27,30,31)). For the article by Mahevas *et al.* (29), one of us (DR) had contact with one of the authors (B Godeau) who told him that it was the methodologist (P Ravaud) who did not want to carry out the statistical tests demonstrating the superiority of dual therapy over the control group (death or transfer to ICU, 0/15 versus 16/63, bilateral Mid-P exact test p = .02).

Overall, and as previously published, the relevance of the analysis of important medical data depends on clinical accuracy (4). Indeed, the discrepancy between clinicians and epidemiologists reflects a major trend, that of the analysis of large medical data, with database warehouse more or less well filled by individuals who are not directly included in the work reported. This analysis is unrelated to the observations made by physicians who are in direct contact with patients and which lead to divergent interpretations and opposite conclusions, which are of real interest and show that the world predicted by Baudrillard (39); that of a parallel world of numerical analysis completely disconnected from reality; is being born.

Under these conditions, a meta-analysis allowing for the combination of different studies makes it possible to identify a general trend. This makes it possible to reconcile the chloroquine derivative efficacy that many doctors have perceived with the results of the first published studies. This meta-analysis is based on several studies, including four RCTs, and identifies a favorable trend toward the benefit of chloroquine derivatives in the treatment of COVID-19 patients, enabling us to make a grade I recommendation for its use against the disease.

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**Funding**

This work was funded by ANR-15-CE36-0004-01 and by ANR "Investissements d'avenir", Méditerranée infection 10-IAHU-03, and was also supported by Région Provence-Alpes-Côte d'Azur. This work had received financial support from the Mediterranean Infection Foundation.

**Declaration of competing interest**

The authors declare no competing interests. Funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Our group used widely available generic drugs distributed by many pharmaceutical companies.

**Acknowledgments**

We thank Christian Devaux for helpful interactions and Fanyu Huang for Chinese to English translation of the study by Chen J *et al.* (14).

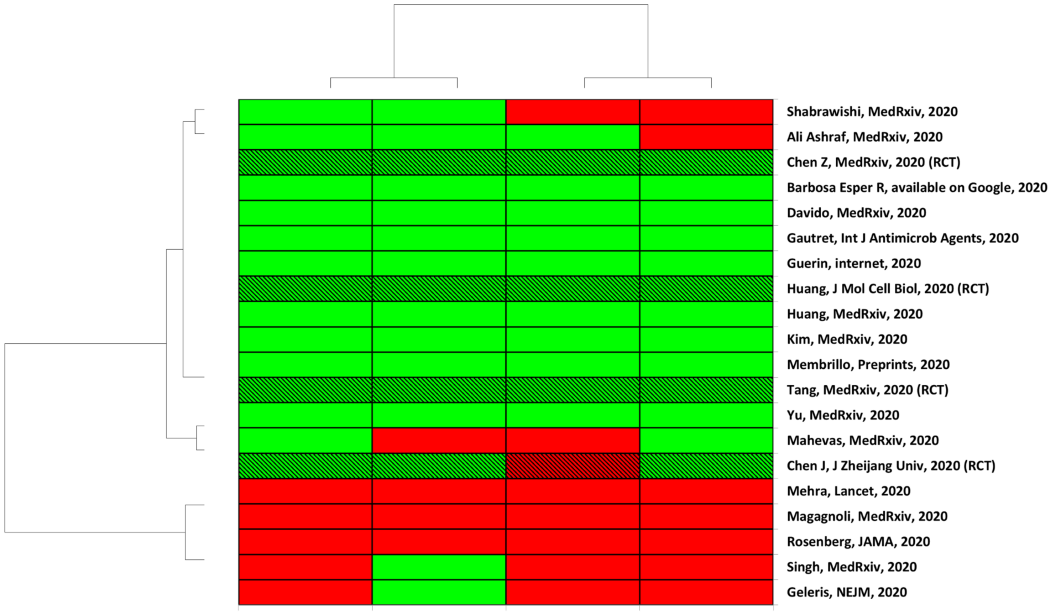
**Figure legends**

**Figure 1. Unsupervised analysis evidencing an association between big data studies, inaccurate treatment protocol, conflict of interest and absence of beneficial effect of chloroquine derivative**

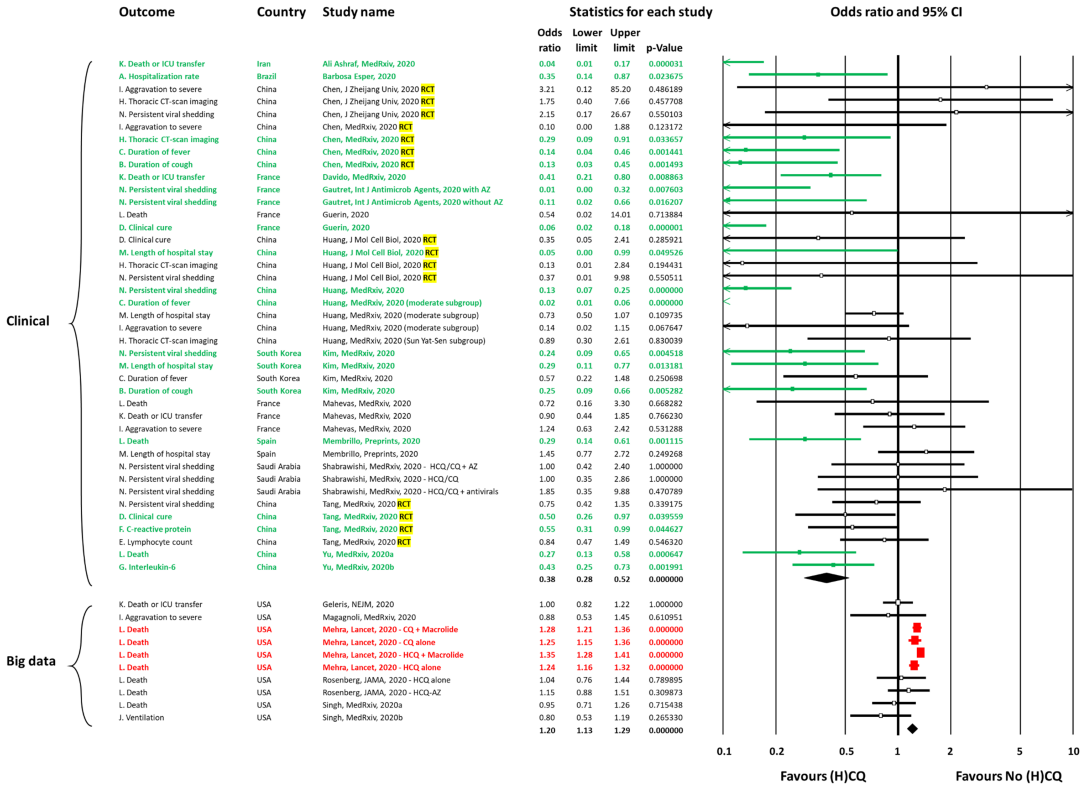
RCT: randomized controlled trial (hatched lines), Pro : study reporting a favourable effect of chloroquine derivative, Con: study that report no or deleterious effet, Clinical : study performed by physician who take care of patients, Big data: study performed by specialists in data analysis who do not take care of patients, Detailed treatment: therapeutic protocol detailed in the method with dosage for 48 hours before outcome assessment. Three among four RCTs found a beneficial effect.

**Figure 2. Forest plot of meta-analysis on the effect of chloroquine derivatives in COVID-19 infected patients**

CI: confidence interval, ICU: intensive care unit, CT-scan: computed tomography scanner, HCQ: hydroxychloroquine, CQ: chloroquine, AZ: azithromycin, RCT: randomized controlled trial, (H)CQ: chloroquine derivatives (hydroxychloroquine (HCQ) or chloroquine (CQ)).




| | | | | |
|---|---|---|---|---|
| Association with Pro/Con | 5/5 vs 3/15 | 4/4 vs 4/16 | | 6/7 vs 2/13 |
| Bilateral Mid-P exact test | p = .004 | p = .01 | | p = .004 |




| | Outcome | Country | Study name | Odds ratio | Lower limit | Upper limit | p-Value |
|---|---|---|---|---|---|---|---|
| Clinical | K. Death or ICU transfer | Iran | Ali Ashraf, MedRxiv, 2020 | 0.04 | 0.01 | 0.17 | 0.000031 |
| | A. Hospitalization rate | Brazil | Barbosa Esper, 2020 | 0.35 | 0.14 | 0.87 | 0.023675 |
| | I. Aggravation to severe | China | Chen, J Zhejiang Univ, 2020 RCT | 3.21 | 0.12 | 85.20 | 0.486189 |
| | H. Thoracic CT-scan imaging | China | Chen, J Zhejiang Univ, 2020 RCT | 1.75 | 0.40 | 7.66 | 0.457708 |
| | N. Persistent viral shedding | China | Chen, J Zhejiang Univ, 2020 RCT | 2.15 | 0.17 | 26.67 | 0.550103 |
| | I. Aggravation to severe | China | Chen, MedRxiv, 2020 RCT | 0.10 | 0.00 | 1.88 | 0.123172 |
| | H. Thoracic CT-scan imaging | China | Chen, MedRxiv, 2020 RCT | 0.29 | 0.09 | 0.91 | 0.033657 |
| | C. Duration of fever | China | Chen, MedRxiv, 2020 RCT | 0.14 | 0.04 | 0.46 | 0.001441 |
| | B. Duration of cough | China | Chen, MedRxiv, 2020 RCT | 0.13 | 0.03 | 0.45 | 0.001493 |
| | K. Death or ICU transfer | France | Davido, MedRxiv, 2020 | 0.41 | 0.21 | 0.80 | 0.008863 |
| | N. Persistent viral shedding | France | Gautret, Int J Antimicrob Agents, 2020 with AZ | 0.01 | 0.00 | 0.32 | 0.007603 |
| | N. Persistent viral shedding | France | Gautret, Int J Antimicrob Agents, 2020 without AZ | 0.11 | 0.02 | 0.66 | 0.016207 |
| | L. Death | France | Guerin, 2020 | 0.54 | 0.02 | 14.01 | 0.713884 |
| | D. Clinical cure | France | Guerin, 2020 | 0.06 | 0.02 | 0.18 | 0.000001 |
| | D. Clinical cure | China | Huang, J Mol Cell Biol, 2020 RCT | 0.35 | 0.05 | 2.41 | 0.285921 |
| | M. Length of hospital stay | China | Huang, J Mol Cell Biol, 2020 RCT | 0.05 | 0.00 | 0.99 | 0.049526 |
| | H. Thoracic CT-scan imaging | China | Huang, J Mol Cell Biol, 2020 RCT | 0.13 | 0.01 | 2.84 | 0.194431 |
| | N. Persistent viral shedding | China | Huang, J Mol Cell Biol, 2020 RCT | 0.37 | 0.01 | 9.98 | 0.550511 |
| | N. Persistent viral shedding | China | Huang, MedRxiv, 2020 | 0.13 | 0.07 | 0.25 | 0.000000 |
| | C. Duration of fever | China | Huang, MedRxiv, 2020 (moderate subgroup) | 0.02 | 0.01 | 0.06 | 0.000000 |
| | M. Length of hospital stay | China | Huang, MedRxiv, 2020 (moderate subgroup) | 0.73 | 0.50 | 1.07 | 0.109735 |
| | I. Aggravation to severe | China | Huang, MedRxiv, 2020 (moderate subgroup) | 0.14 | 0.02 | 1.15 | 0.067647 |
| | H. Thoracic CT-scan imaging | China | Huang, MedRxiv, 2020 (Sun Yat-Sen subgroup) | 0.89 | 0.30 | 2.61 | 0.830039 |
| | N. Persistent viral shedding | South Korea | Kim, MedRxiv, 2020 | 0.24 | 0.09 | 0.65 | 0.004518 |
| | M. Length of hospital stay | South Korea | Kim, MedRxiv, 2020 | 0.29 | 0.11 | 0.77 | 0.013181 |
| | C. Duration of fever | South Korea | Kim, MedRxiv, 2020 | 0.57 | 0.22 | 1.48 | 0.250698 |
| | B. Duration of cough | South Korea | Kim, MedRxiv, 2020 | 0.25 | 0.09 | 0.66 | 0.005282 |
| | L. Death | France | Mahevas, MedRxiv, 2020 | 0.72 | 0.16 | 3.30 | 0.668282 |
| | K. Death or ICU transfer | France | Mahevas, MedRxiv, 2020 | 0.90 | 0.44 | 1.85 | 0.766230 |
| | I. Aggravation to severe | France | Mahevas, MedRxiv, 2020 | 1.24 | 0.63 | 2.42 | 0.531288 |
| | L. Death | Spain | Membrillo, Preprints, 2020 | 0.29 | 0.14 | 0.61 | 0.001115 |
| | M. Length of hospital stay | Spain | Membrillo, Preprints, 2020 | 1.45 | 0.77 | 2.72 | 0.249268 |
| | N. Persistent viral shedding | Saudi Arabia | Shabrawishi, MedRxiv, 2020 - HCQ/CQ + AZ | 1.00 | 0.42 | 2.40 | 1.000000 |
| | N. Persistent viral shedding | Saudi Arabia | Shabrawishi, MedRxiv, 2020 - HCQ/CQ | 1.00 | 0.35 | 2.86 | 1.000000 |
| | N. Persistent viral shedding | Saudi Arabia | Shabrawishi, MedRxiv, 2020 - HCQ/CQ + antivirals | 1.85 | 0.35 | 9.88 | 0.470789 |
| | N. Persistent viral shedding | China | Tang, MedRxiv, 2020 RCT | 0.75 | 0.42 | 1.35 | 0.339175 |
| | D. Clinical cure | China | Tang, MedRxiv, 2020 RCT | 0.50 | 0.26 | 0.97 | 0.039559 |
| | F. C-reactive protein | China | Tang, MedRxiv, 2020 RCT | 0.55 | 0.31 | 0.99 | 0.044627 |
| | E. Lymphocyte count | China | Tang, MedRxiv, 2020 RCT | 0.84 | 0.47 | 1.49 | 0.546320 |
| | L. Death | China | Yu, MedRxiv, 2020a | 0.27 | 0.13 | 0.58 | 0.000647 |
| | G. Interleukin-6 | China | Yu, MedRxiv, 2020b | 0.43 | 0.25 | 0.73 | 0.001991 |
| | | | | **0.38** | **0.28** | **0.52** | **0.000000** |
| Big data | K. Death or ICU transfer | USA | Geleris, NEJM, 2020 | 1.00 | 0.82 | 1.22 | 1.000000 |
| | I. Aggravation to severe | USA | Magagnoli, MedRxiv, 2020 | 0.88 | 0.53 | 1.45 | 0.610951 |
| | L. Death | USA | Mehra, Lancet, 2020 - CQ + Macrolide | 1.28 | 1.21 | 1.36 | 0.000000 |
| | L. Death | USA | Mehra, Lancet, 2020 - CQ alone | 1.25 | 1.15 | 1.36 | 0.000000 |
| | L. Death | USA | Mehra, Lancet, 2020 - HCQ + Macrolide | 1.35 | 1.28 | 1.41 | 0.000000 |
| | L. Death | USA | Mehra, Lancet, 2020 - HCQ alone | 1.24 | 1.16 | 1.32 | 0.000000 |
| | L. Death | USA | Rosenberg, JAMA, 2020 - HCQ alone | 1.04 | 0.76 | 1.44 | 0.789895 |
| | L. Death | USA | Rosenberg, JAMA, 2020 - HCQ-AZ | 1.15 | 0.88 | 1.51 | 0.309873 |
| | L. Death | USA | Singh, MedRxiv, 2020a | 0.95 | 0.71 | 1.26 | 0.715438 |
| | J. Ventilation | USA | Singh, MedRxiv, 2020b | 0.80 | 0.53 | 1.19 | 0.265330 |
| | | | | **1.20** | **1.13** | **1.29** | **0.000000** |