Hydroxychloroquine and Azithromycin as a Treatment of COVID-19: Results of an Open-Label Non-Randomized Clinical Trial: Response to criticisms

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We thank the authors for comments provided for our article (1-3), but we would like to clarify key points for the story of this manuscript (4) that are critical in the context of COVID-19 outbreak and for the perspective of this work. When COVID-19 starts around the world the Editor-In-Chief of the Journal International Journal of Antimicrobial Agents (JM. Rolain) asked colleagues (D. Raoult, PR. Hsueh, and S. Stefani) to launch a special issue in the journal to create a real-time rapid debate around this emerging disease with special regards to therapeutic options (5). Our preliminary paper (4) in this way was relatively trivial i.e reported, in an emergency situation, a comparative analysis between a small group treated with hydroxychloroquine and another small group not treated with hydroxychloroquine showing a significant decrease of viral shedding after 6 days of therapy.

Surprisingly, despite the very small size of the group, the addition of azithromycin made a difference on the endpoint we chose, which is the disappearance of the viral load in the pharynx that is the only data that can be analyzed on a small group (6). Indeed, neither mortality, nor the passage in intensive care unit, nor the duration of the treatment can be evaluated on such a small group (6). This preliminary information was essential in our opinion especially as it confirmed the preliminary *in vitro* and *in vivo* results against SARS-CoV-2 announced by the Chinese (7-9), also confirming previous *in vitro* reports on the anti-SARS-CoV-1 coronavirus activity dating back to 2004 (10-13). This preliminary report paved the way for work testing its reproducibility.

On the therapeutic level, the hydroxychloroquine + azithromycin combination was found to be the most effective (4) consistent with *in vitro* synergistic antiviral activity reported in our laboratory (14,15). Azithromycin had already, contrary to what one of the authors says, been tested effectively on Zika (16, 17), so we knew that it had an antiviral action. With regard to our seminal paper on *in vivo* anti-SARS-CoV-2 activity of hydroxychloroquine (4), we were subjected to unprecedented violence. I (DR) was asked to

confess that I had a relationship and a conflict of interest with Sanofi, which is laughable when you use generics and you have had no relationship with the pharmaceutical industry at all at IHU (our center) for 5 years. The second thing is that I (DR) was harassed to give all the evidence to show that this was done after the agreement of our government, the evaluation by the Committee for the Protection of Individuals, and that it was done in all regularity (validated by ANSM, the French FDA, available online in the EU Clinial Trial Register Page, EudraCT number: 2020-000890-25). Subsequently, we were threatened for retractation of this article, with no justification other than the opinion of people who were fiercely hostile to the use of hydroxychloroquine. It should be noted that this paper is now by far the most cited paper in the literature on the treatment of COVID-19, exceeding 2,500 citations in Google Scholar.

As a result of this paper, half of the world's population lives in countries where hydroxychloroquine with or without azithromycin is largely prescribed against COVID-19, this currently concerns more than 4.5 billion people (18). On the other hand, methodological problems and problems of scientific misconduct with non-declaration of conflict of interest have multiplied for therapeutics in the best journals which ended up with the retraction of a paper (19).

Over the past few decades, randomized controlled trials (RCTs) have been considered the ultimate in defining the best treatment for a disease, especially in large international multi-center studies largely funded by pharmaceutical companies. This is not true because there are no significant differences in effect estimates between observational studies and RCTs, regardless of the specific design of the observational studies, heterogeneity or inclusion of studies of pharmacological interventions as demonstrated by a Cochrane review that analyzed 1583 meta-analyses covering 228 different medical conditions (20). RCTs introduce several biases (21), including that the physicians and patients included in these trials are not the same

as those included in observational studies (selection bias). Furthermore, the fact that RCTs on the same disease produce heterogeneous results with different directions of the effect shows that these approaches are not accurate (22) and does not prevent the effect of confounding factors. This inaccuracy has also been illustrated by the fact that the range for point estimate was wider for randomized, controlled trials than for observational studies in a meta-analysis of 99 reports on 5 different medical conditions from 5 major medical journals (Annals of internal medicine, BMJ, JAMA, the Lancet, and the New England Journal of Medicine) (23).

The limited role of RCTs in clinical practice is also confirmed by the fact that the majority (>80%) of infectious disease recommendations are not based on any placebo-controlled RCT. For example, the recommendations in the Infectious Diseases Society of America (IDSA) clinical practice guidelines are primarily based on evidence from non-randomized studies or expert opinion. Evidence based on at least one RCT makes up only 16% of the recommendations (24). This is also the case, for example, for quinine for malaria, penicillin, treatment of syphilis, treatment of typhoid, Q fever, Whipple's disease, and most vaccines, including rabies vaccine.

Beyond RCTs, big data studies were presented as a new reference. Here, we report an update of a meta-analysis (25) that highlights the Simpson's paradox (26): Big data studies, which "pool" raw data from very different groups, produce very heterogeneous and inconsistent results, whereas clinical studies, conducted by physicians who see patients, have consistent results. Overall, all of this suggests that well-conducted observational studies conducted by physicians who see patients and who know the disease are the best approach to control confounding factors and to define optimal patient management, particularly in an acute fatal pandemic disease such as COVID19 (21,23).

Finally, we have recently carried out a meta-analysis of all the work done on hydroxychloroquine (25) that is upgraded in this response. Here, we specifically focused on

mortality and viral shedding persistence, including two new randomized controlled trial reporting a favorable effect on viral shedding (27,28) (Figure 1). Importantly, while the conflict has been particularly violent in France and the United States, 5 studies from both these countries have shown that hydroxychloroquine reduces rate of hospitalization, length of hospitalization, mortality, and viral shedding in 4,642 (29), 3,737 (30), 2,820 (31), 2,541 (32) and 518 (33) patients. The methods are detailed in the supplementary data.

This new meta-analysis (Figure 1) included, for the mortality outcome, 48,655 patients (including 29,153 treated by a chloroquine derivative) from 31 studies in 11 countries (Andorra (34), Belgium (35), Brazil (36), China (37), Egypt (38), France (29,30,39-43), Italy (44-47), Iran (48), Saudi Arabia (49), Spain (50-52), USA (31-33,53-57), and two multinational teams (58,59). Studies assessing the death outcome but excluded from the present analysis and reasons for exclusion are detailed in Supplementary Table 1. Data extracted from the included studies for the mortality outcome are reported in Supplementary Table 2. A two-fold decrease of the risk of death was confirmed in clinical studies (number of comparisons (n) = 23, odds ratio 0.56, 95% confidence interval (95%CI) 0.48 – 0.65, p = 7.47×10^{-13}) and among big data studies (n = 14, OR = 0.89, 95%CI 0.81 – 0.98, p = 0.022 – Figure 1A). Heterogeneity was significant between clinical and big data studies (Q-value 39.8, p = 2.8×10^{-10}). Effect size was consistent among clinical studies (I^2 = 29%, p = 0.09) but not among big data studies (I^2 = 78%, p = 7.1×10^{-8}). Indeed, for instance, a big data study (31) recently reported a very significant two-fold decrease in mortality in 2,820 patients from the 8 hospitals of the Mount Sinai Health System (New York, USA). This result contrasts with other big data studies (29,53,57). Despite substantial heterogeneity, a significant summary effect was observed when including all comparisons from all included studies (n = 37, OR 0.78, 95%CI 0.72 - 0.85, p = 1.1×10^{-8}). Exclusion of the study from our center (30) did not modify neither the overall effect (n = 36, OR = 0.76, 95%CI 0.69 – 0.84, p = 6.0×10^{-8}) nor the

two-fold decrease in the risk of death among 18 clinical studies from other centers (n = 22, OR 0.55, 95%CI 0.46 - 0.65, $p = 2.0x10^{-11}$).

Looking at persistent viral shedding, a total of 5,204 patients (3,765 treated by a chloroquine derivative) from 12 studies from only 6 countries were included (5 from China (27,60-63), 2 from France (30,42), 1 from Pakistan (28), 1 from Saudi Arabia (64), 2 from South Korea (65,66) and 1 from Taiwan (67). Studies assessing the viral shedding outcome but excluded from the present analysis and reasons for exclusion are detailed in Supplementary Table 3. Data extracted from the included studies for the viral shedding outcome are reported in Supplementary Table 4. Overall, a substantial heterogeneity was found among all study ($I^2 = 78\%$), and this heterogeneity remained unchanged after excluding the only one found as a big data study associated with unfavorable outcome (66). Meta-analysis of clinical studies evidenced a significant two-fold decrease of the risk of viral persistence (13 comparisons, OR 0.50, 95%CI 0.32 – 0.79, p = 0.003, Figure 1B). Exclusion of our study (30) did not change the effect size (n = 12, OR = 0.48, 95% CI 0.26 – 0.87). Strikingly, none of the studies from USA assessed the virus persistence (68).

This new meta-analysis shows that, apart from the unverifiable work that did not assess virological outcome and carried out by people who had conflicts of interest with the pharmaceutical industry (69), the body of publications shows that hydroxychloroquine therapy is significantly and reproducibly correlated with a two-fold decrease in both mortality and viral shedding.

In practice, our seminal work (4) has benefited from a massive diffusion despite a profusion of papers that have not been verified but accepted each time they had a negative position towards hydroxychloroquine (6,68). However, the facts being stubborn, the accumulation of publications showing that hydroxychloroquine is effective following our paper leaves no doubt that this preliminary study did indeed paved the way for a therapeutic

strategy that is now being generalized throughout the world, and whose favorable results have been replicated several times. In addition, a group of American and Italian experts recently recommended the use of hydroxychloroquine and azithromycin in COVID-19 outpatients at the early stage of the infection (70).

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Declaration of competing interest

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Authors' contributions statement:

Writing – original draft: MM, PG & DR

Writing – review & editing: JCL, PC, PP, JMR & DR

Conceptualization: DR

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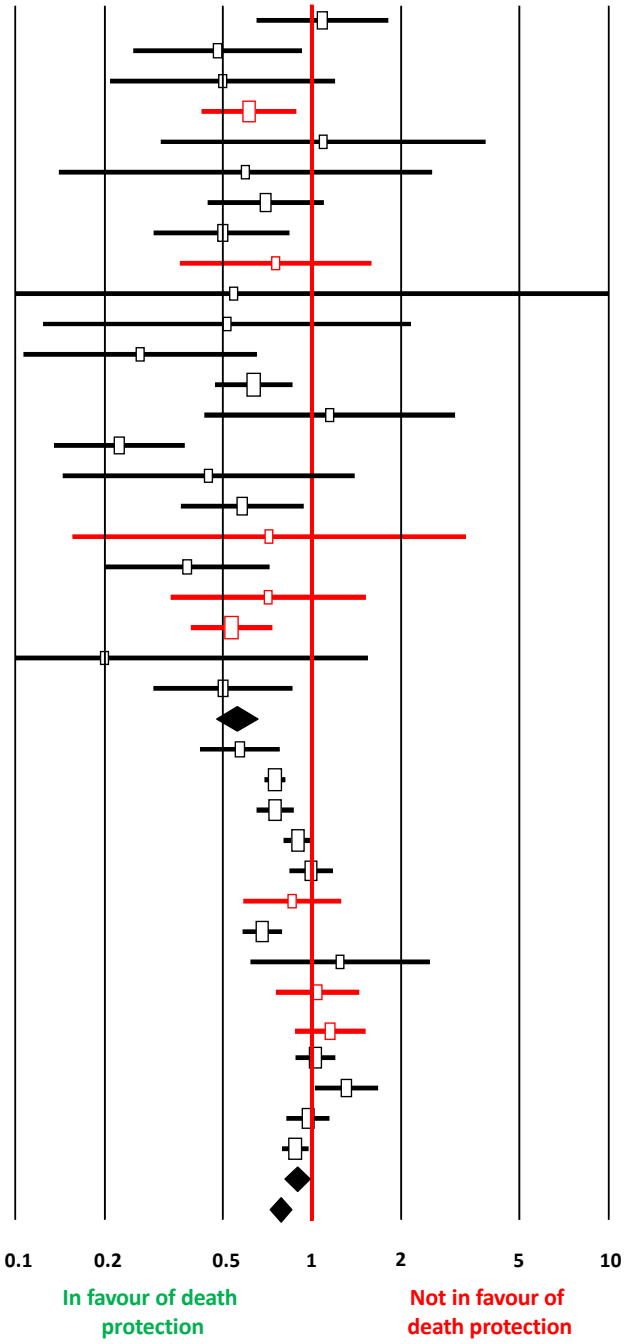
Figure 1. Meta-analysis on chloroquine derivatives against COVID-19

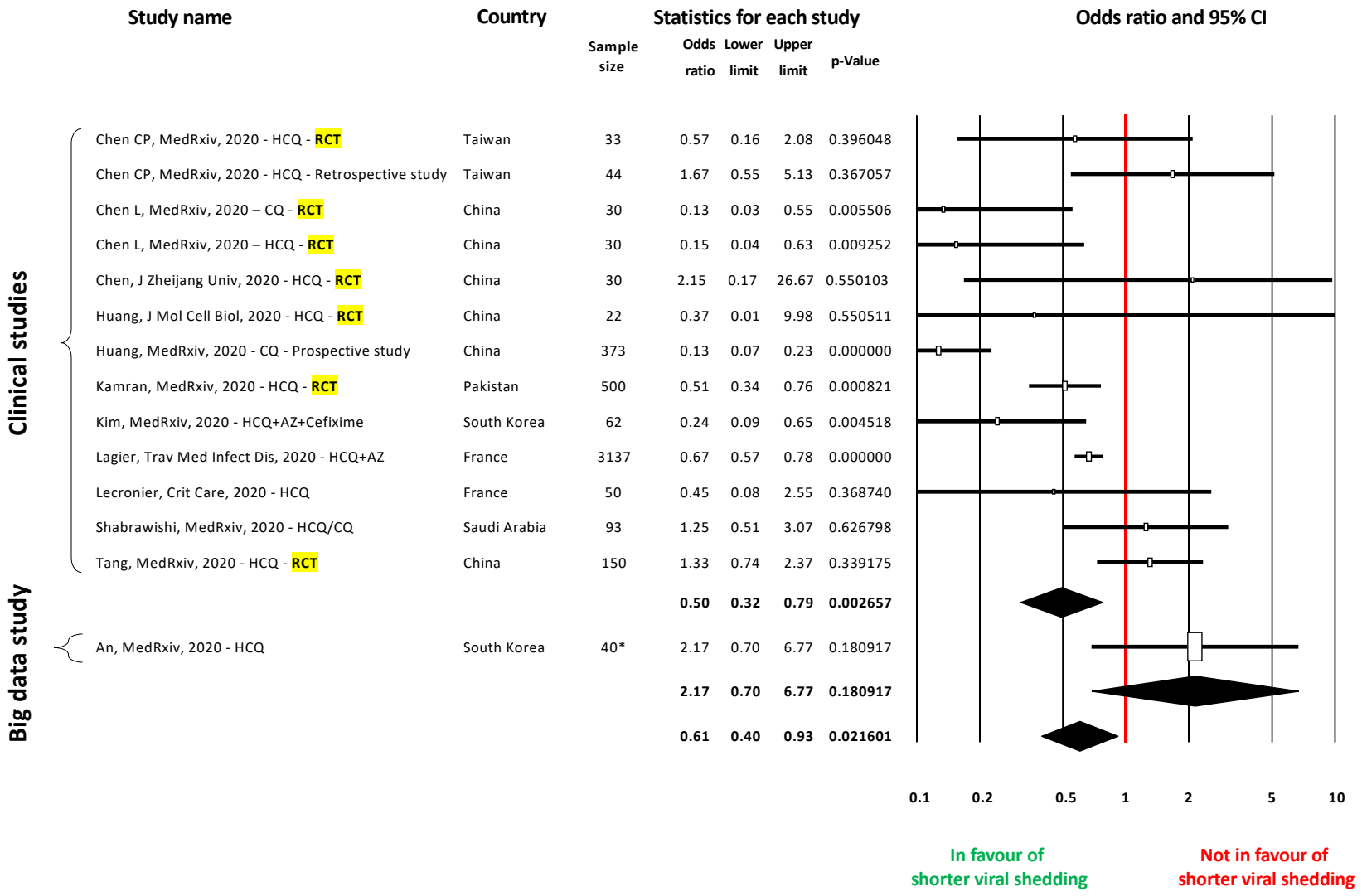
A. Mortality, B. Viral shedding. CI: confidence interval, HCQ: hydroxychloroquine, CQ: chloroquine, AZ: Azithromycin, RCT: randomized controlled trial. This meta-analysis was performed with a random-effects model using Comprehensive Meta-Analysis v3 (Biostat, Englewood, NJ, USA). Randomized controlled trials are labeled "RCT" (highlighted in yellow) and studies whose authors reported conflicts of interests are written in red. *In this study, 226 patients were included but only 40 matched patients were included in the multivariate statistical analysis.

A. Mortality

	Study name	Country	Sample size	Odds ratio	Lower limit	Upper limit	p-Value
Clinical studies	Abd-Elsalam, Am J Trop Med Hyg, 2020 – HCQ - RCT	Egypt	194	1.08	0.65	1.81	0.756693
	Alamdari, Tohoku J Exp Med, 2020 - HCQ	Iran	459	0.48	0.25	0.92	0.027913
	Alberici, Kidney International, 2020 - HCQ	Italy	94	0.50	0.21	1.20	0.118956
	Arshad, Int J Infect Dis, 2020 – HCQ+/-AZ	USA	380	0.61	0.43	0.88	0.008954
	Cavalcanti, N Eng J Med, 2020 - HCQ alone - RCT	Brazil	504	1.09	0.31	3.84	0.892228
	Cavalcanti, N Engl J Med, 2020 - HCQ+AZ - RCT	Brazil		0.60	0.14	2.54	0.484016
	D'Arminio Monforte, IJID, 2020 - HCQ alone	Italy	383	0.70	0.45	1.09	0.117676
	D'Arminio Monforte, IJID, 2020 - HCQ+AZ	Italy		0.50	0.29	0.84	0.008904
	Goldman, N Eng J Med, 2020 - RCT - HCQ	Multinational	397	0.75	0.36	1.59	0.457240
	Guerin, Asian J Med Health, 2020 - HCQ+AZ	France	54	0.54	0.02	14.01	0.713884
	Heras, Researchsquare, 2020 - HCQ alone	Andorra	100	0.52	0.12	2.15	0.364516
	Heras, Researchsquare, 2020 - HCQ+AZ	Andorra		0.26	0.11	0.65	0.003894
	Lagier, Trav Med Infect Dis, 2020 - HCQ+AZ	France	702	0.64	0.47	0.86	0.002990
	Lauriola, Clin Translat Sci, 2020 - HCQ alone	Italy	377	1.15	0.43	3.03	0.781317
	Lauriola, Clin Translat Sci, 2020 - HCQ+AZ	Italy		0.22	0.14	0.37	0.000000
	Lecronier, Critical Care, 2020 - HCQ	France	60	0.45	0.14	1.39	0.164805
	Ly, IHU Preprints, 2020 - HCQ+AZ	France	226	0.58	0.36	0.94	0.025830
	Mahevas, MedRxiv, 2020 - HCQ	France	181	0.72	0.16	3.30	0.668282
	Membrillo de Novales, Preprints, 2020 - HCQ	Spain	166	0.38	0.20	0.72	0.002955
	Paccoud, Clin Infect Dis, 2020 - HCQ	France	89	0.71	0.33	1.52	0.378609
	Pinato, Cancer Research, 2020 - HCQ	Multinational	628	0.54	0.39	0.73	0.000099
	Scholz, Preprints, 2020 - HCQ+AZ+Zn	USA	518	0.20	0.03	1.54	0.122632
	Yu, Sci China Life Sci, 2020 - HCQ	China	550	0.50	0.29	0.86	0.011961
			6062	**0.56**	**0.48**	**0.65**	**0.000000**
Big data studies	Bernaola, MedRxiv, 2020 - HCQ	Spain	1645	0.57	0.42	0.78	0.000369
	Catteau, Int J Antimicrob Agents, 2020 - HCQ	Belgium	8075	0.75	0.69	0.81	0.000000
	Di Castelnuovo, Eur J Intern Med, 2020 - HCQ	Italy	3451	0.75	0.65	0.87	0.000086
	Gonzalez, MedRxiv, 2020 – HCQ	Spain	9617	0.90	0.80	1.00	0.056994
	Ip, MedRxiv, 2020 – Inpatients - HCQ	USA	2512	0.99	0.84	1.17	0.929993
	Ip, MedRxiv, 2020 – Outpatients - HCQ	USA	1067	0.86	0.59	1.25	0.426891
	Mikami, J Gen Intern Med, 2020 - HCQ	USA	2820	0.68	0.58	0.79	0.000001
	Roomi, J Med Internet Res, 2020 - HCQ	USA	176	1.24	0.62	2.49	0.539415
	Rosenberg, JAMA, 2020 - HCQ alone	USA	1227	1.04	0.76	1.44	0.789895
	Rosenberg, JAMA, 2020 - HCQ+AZ	USA		1.15	0.88	1.51	0.309873
	Sbidian, MedRxiv, 2020 - HCQ alone	France	4642	1.03	0.88	1.20	0.729985
	Sbidian, MedRxiv, 2020 - HCQ+AZ	France		1.31	1.02	1.67	0.030990
	Singh, MedRxiv, 2020 - HCQ	USA	1820	0.97	0.82	1.15	0.719963
	Sulaiman, MedRxiv, 2020 - HCQ	Saudi Arabia	5541	0.88	0.79	0.97	0.011996
			42593	**0.89**	**0.81**	**0.98**	**0.021899**
			48655	**0.78**	**0.72**	**0.85**	**0.000000**



B. Viral shedding



Hydroxychloroquine and Azithromycin as a Treatment of COVID-19: Results of an Open-Label Non-Randomized Clinical Trial: Response to criticisms

SUPPLEMENTARY DATA

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Supplementary 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 (research updated on September, 9, 2020) 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. An overview of most of the screened studies can be accessed at https://c19study.com/. The following outcomes were considered: death and persistent viral shedding as assessed by PCR.

Only studies comparing a group of COVID19 patients, mandatorily confirmed by PCR, treated with a chloroquine derivative to a control group without chloroquine derivatives were included. Studies must provide the number of treated and untreated individuals. 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

analyzing safety, efficacy as a prevention, data provided as a webpage without an article format (such as a tweet), were also excluded. Studies without confirmation of the diagnosis by RT-PCR were excluded. For the “mortality” outcome, studies without any death were excluded. For the “viral shedding” outcome, only studies reporting at least the proportion of positive PCR were included. Studies assessing only viral load without data on the proportion of positive samples 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.

The meta-analysis was performed with a randomized model using Comprehensive Meta-Analysis v3 (Biostat, Englewood, NJ, USA) as recommended by Borenstein *et al.* (1). 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). The most adjusted effect size reflecting the greatest control for potential confounding factors was extracted. Heterogeneity was considered substantial when $I^2 > 50\%$. A p-value < 0.05 was considered significant.

Supplementary Table 1. Studies assessing the death outcome (at least one death) but excluded and reason for exclusion

Study	Reason
Ahmad, MedRxiv, 2020 (2) https://www.medrxiv.org/content/ 10.1101/2020.05.18.20066902v1	Number of treated and untreated patients not provided
Ayerbe, J Thromb Thrombolysis, 2020 (3) https://link.springer.com/article/ 10.1007%2Fs11239-020-02162-z	Possible duplicate with Mateos Gonzales, MedRxiv, 2020
Calik Basaran, Turk J Med Sci, 2020 (4) https://pubmed.ncbi.nlm.nih.gov/32718127/	Diagnosis not confirmed by PCR
Chowdhury, Researchsquare, 2020 (5) https://www.researchsquare.com/ article/rs-38896/v1	Control group treated by doxycycline and ivermectin
Fried, Clin Infect Dis, 2020 (6) https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1268/5898276	Confounding by indication "Patients treated with hydroxychloroquine were more likely to be on mechanical ventilation compared to those who did not receive hydroxychloroquine (24.9% vs 12.2%)." (1054/4232 vs 913/7489, bilateral khi square test, $p < 0.0001$)
Horby et al., MedRxiv, 2020 (7) https://www.medrxiv.org/content/ 10.1101/2020.07.15.20151852v1	Toxic doses (2400 mg fir the first 24 hours), PCR confirmation was not mandatory

Kelly, Br Pharmcol Soc, 2020 (8) https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/bcp.14482	Confounding by indication : No approach to control for confounding and treated group with higher CRP (81.5 vs 28, p < .0001), higher FiO2 requirement median day 0 (24% vs 21%, p < .0001).
Magagnoli, Med, 2020 (9,10) https://www.cell.com/med/pdf/S2666-6340(20)30006-4.pdf	Lymphopenia more frequent in the treated group / HCQ started after intubation / Azithromycin given to 30% of control group
McGrail, MedRxiv, 2020 (11) https://www.medrxiv.org/content/10.1101/2020.07.17.20156521v1	Confounding by indication “The latter two groups were significantly more ill than the untreated group”
Peters, MedRxiv, 2020 (12) https://www.medrxiv.org/content/10.1101/2020.08.14.20173369v1	HCQ initiation when patients deteriorated
Rivera, Cancer Discovery, 2020 (13) https://cancerdiscovery.aacrjournals.org/content/early/2020/07/21/2159-8290.CD-20-0941	Confounding by indication
Sanchez Alvarez, Nefrologia, 2020 (14) https://www.sciencedirect.com/science/article/pii/S201325142030050X	Number of treated and untreated patients not provided

Skipper, Annals of Internal Medicine, 2020 (15) https://www.acpjournals.org/doi/10.7326/M20-4207	Only 58% of participants received SARS-CoV-2 testing because of severe U.S. testing shortages.
Synolaki, MedRxiv, 2020 (16) https://www.medrxiv.org/content/ 10.1101/2020.09.05.20184655v1	Number of treated and untreated patients not provided for the different groups of severity

Supplementary Table 2. Chloroquine derivatives and COVID19 mortality – Data extracted (as of September 2020, 21)

	Country	N treated	N untreated	Data in the manuscript	Data entered in the software
CLINICAL STUDIES (POSSIBLE CONFLICT OF INTEREST) (Reference)					
Abd-Elsalam, Am J Trop Med Hyg, 2020 (No) (17)	**Egypt**	**97**	**97**	Table 4. Univariate regression Hydroxychloroquine treatment OR 0.824 (0.243 - 2.797) P = 0.757	**Positive direction P = 0.757**
Alamdari, Tohoku J Exp Med, 2020 (No) (18)	**Iran**	**427**	**32**	Table 4. Therapies and outcomes. P = 0.028	**Negative direction P = 0.028**
Alberici, Kidney International, 2020 (No) (19)	**Italy**	**72**	**22**	Table 3 | Univariate analyses of the association between clinical characteristics and the risk of ARDS or death in hemodialysis patients with SARS-CoV-2 infection. Hydroxychloroquine: outcome death OR 0.44 (0.16–1.24) p = 0.12	**Negative direction P = 0.12**
Arshad, Int J Infect Dis, 2020 (I.B. received speakers' bureau honoraria from Gilead) (20)	**USA**	**190 (propensity score matched patients)**	**190 (propensity score matched patients)**	Table 4. Propensity Matched Cox Regression Result for Mortality Prediction	**Negative direction P = 0.009**

				Given HCQ p-value = 0.009 **, Hazard Ratio 0.487 – (0.285 0.832)	
Cavalcanti, N Eng J Med, 2020 – HCQ alone (No) (21)	**Brazil**	**159**	**173**	Table 2. Primary and Secondary Outcomes (Modified Intention-to-Treat Population).* Death 5/159 vs 5/173	**5/159 vs 5/173**
Cavalcanti, N Eng J Med, 2020 – HCQ+AZ (No) (21)	**Brazil**	**172**	**173**	Table 2. Primary and Secondary Outcomes (Modified Intention-to-Treat Population).* Death 3/172 vs 5/173	**3/172 vs 5/173**
D'arminio Monforte, IJID, 2020 – HCQ alone (No) (22)	**Italy**	**197**	**92**	Table 1 Unadjusted and adjusted marginal relative hazards of in-hospital mortality Adjusted HR 0.66 (0.39, 1.11), p = 0.118	**Negative direction p = 0.118**
D'arminio Monforte, IJID, 2020 – HCQ+AZ (No) (22)	**Italy**	**94**	**92**	Table 1 Unadjusted and adjusted marginal relative hazards of in-hospital mortality Ajusted HR 0.44 (0.24, 0.82), p = 0.009	**Negative direction P = 0.009**
Goldman, N Eng J Med, 2020 (Funded by Gilead Sciences) (23)	**Multinational**	**109**	**288**	Table S3. Baseline Predictors of Time to Clinical Improvement (with p-values <0.2) / Patients who Died Before Achieving Clinical Improvement (Competing Risks)	**10/109 vs 34 / 288**

				N (%) / Received hydroxychloroquine yes 10 / 109 vs no 34 / 288	
Guerin, Asian J Med Health, 2020 (No) (24)	**France**	**20**	**34**	"One patient, a man of 82-year-old without comorbidities in the NST group died suddenly;"	**0/20 vs 1/34**
Heras, Researchsquare, 2020 – HCQ+AZ (No) (25)	**Andorra**	**70**	**21**	Table 3 Risk factors associated with COVID-19 mortality on multivariate analysis Treatment H+A OR 0.044 p = 0.004	**Negative direction** **P = 0.004**
Heras, Researchsquare, 2020 – HCQ alone (No) (25)	**Andorra**	**9**	**21**	Table 3 Risk factors associated with COVID-19 mortality on multivariate analysis Treatment H OR 0.32 p = 0.369	**Negative direction** **P = 0.369**
Lagier, Trav Med Infect Dis, 2020 (No) (26)	**France**	**503**	**199**	Table 5 Age stratified multivariable analyses adjusted on comorbidities and severity of the disease addressing associations between treatment (HCQ-AZ ≥ 3 days) and clinical outcomes/viral shedding clearance (n = 3,737). Weighted Cox regression on	**Negative direction** **P = 0.003**

				Unmatched sample (n = 702) Hazard ratio 0.49 (0.31–0.79), p = 0.0030	
Lauriola, Clinical Transl Sci, 2020 – HCQ alone (No) (27)	**Italy**	**17**	**63**	Table 2. Multivariable Cox proportional hazard regression analysis of factors associated with in-hospital death. HCQ (vs. no treatment) 1.108 (0.536-2.293) p = 0.782	**Positive direction** **P = 0.782**
Lauriola, Clinical Transl Sci, 2020 – HCQ+AZ (No) (27)	**Italy**	**297**	**63**	Table 2. Multivariable Cox proportional hazard regression analysis of factors associated with in-hospital death. HCQ + azithromycin (vs. no treatment) HR 0.265, 95%CI 0.171-0.412, p<0.001	Exact p-value calculated* : **p = 6.67924E-09**
Lecronier, Critical care, 2020 (No) (28)	**France**	**38**	**22**	Table 2 Primary and secondary outcomes - 28-day mortality, n (%) standard of care 9/22 vs Lopinavir/ritonavir 7/20 vs hydroxychloroquine 9/38, p = 0.35	**9/38 vs 9/22**
Ly, IHU preprints, 2020 (No) (29)	**France**	**116**	**110**	Table 3. Associations between multiple factors and SARS-CoV-2 death among 226 infected elderly	**Negative direction** **P = 0.026**

				residents (univariate and multivariate analysis) / HCQ/AZ treatment for at least 3 days (226) / Multivariate 0.39 [0.17-0.89] 0.026	
Mahevas, MedRxiv, 2020 (in the final corrected version of the MS published in BMJ : SG reports personal fees and non-financial support from Gilead Sciences / FXL has received personal fees from Gilead / RL reports non-financial support from Eumedica SA, non-financial support from Gilead Sciences / CO reports non-financial support from MSD, non-financial support from Janssen, non-financial support from CSL Behring, non-financial support from Gilead / JMP reports personal fees from Abbvie, personal fees from Gilead / FS reports personal fees from Gilead Sciences /) (30)	**France**	**92**	**89**	Supplementary data 4: Sensitivity analyses* Trimmed sample that was truncated at 10% of the extreme weights.	Events were recalculated and this is explaine in : https://www.mediterranee-infection.com/correction-scientifique/ **3/92 vs 4/89**
Membrillo de Novales, Preprints, 2020 (No) (31)	**Spain**	**123**	**43**	Table 4. Significant outcomes of the multi-variant analysis of survival - HCQ treatment P = 0,003 - Exp(B) 0,070 (0,012-0,402)	**Negative direction P = 0.003**

Paccoud, Clin Infect Dis, 2020 (eurosfordocs reported several authors with conflict of interests particularly Vincent Calvez, Marc Antoine Valantin, Romain Palich – each of them received more than 10,000 euros from Gilead) (32)	**France**	**43**	**46**	Supplementary Data table 2: Results of sensivity analyses - Other sensivity analyses: results on the Secondary population - Time-to-event outcomes evaluated from admission – Death - IPTW-weighted analysis HR 0.52 [0.12; 2.29], p = 0.38	**Negative direction** **P = 0.38**
Pinato, Cancer Research, 2020 (MP has declared consulting/advisory role for Gilead and Bayer /) (33)	**Multinational**	**182**	**446**	Table 3. Model-adjusted risk of mortality complemented by restricted mean survival time analysis according to type of anti-Covid-19 therapy in patients with cancer and SARS-Cov-2 infection – Therapy Antimalarials only (n=182) vs no drug (n=446) / Restricted mean survival time (RMST) analyses: Cox proportional model : HR 0.41 (0.26-0.66) p<0.0001	**Negative direction** **P = 0.0001**
Scholz, Preprints, 2020 (No) (34)	**USA**	**141**	**377**	Table 7. Clinical Outcome in the Treated Patient Group versus the Untreated Patient Group / All-cause death 1/141 vs 13/377	**1/141 vs 13/377**

Yu, Sci China Life Sci, 2020 (No) (35)	**China**	**48**	**502**	Table 3 Univariable and multivariable cox proportional hazards model for 60-day fatality after HCQ treatment Adjusted HR (95% CI), 0.36 (0.18–0.75), p = 0.006	**Negative direction** **P = 0.006**
BIG DATA STUDIES					
Bernaola, MedRxiv, 2020 (No) (36)	**Spain**	**1498**	**147**	Table 2: Hazard ratio with 95% confidence intervals and Cohen's d for various treatments before and after propensity-score matching, for their effects on mortality rate. Propensity score matching Hazard ratios HCQ 0.84 ± 0.08	**Negative direction** **P = 0.00037 (*calculated from the ratio 0.84 and confidence interval 0.76-0.92)**
Catteau, Int J Antimicrob Agents, 2020 (No) (37)	**Belgium**	**4542**	**3533**	« Treatment with HCQ alone was in contrast independently associated with decreased risk of in-hospital mortality (Adjusted hazard ratio [HR] 0.684, 95% confidence interval [CI] 0.617–0.758) compared to the no-HCQ group »	**Negative direction** **P* = 1.96xE-12**
Di Castelnuovo, Eur J Intern Med, 2020 (No) (38)	**Italy**	**2634**	**817**	Table 2 Incidence rates and hazard ratios for death in COVID-19 patients, according to hydroxychloroquine use	**Negative direction** **P* = 8.66xE-05**

				Propensity score analysis, inverse probability weighting** (primary analysis) HR 0.70 (0.59 to 0.84)	
Gonzalez, MedRxiv, 2020 (No) (39)	**Spain**	**8448**	**1169**	Table 4. Multivariate analysis of mortality. The effect of each factor is expressed as an Adjusted Odds Ratios (CI 95%). Hydroxychloroquine Adjusted OR 0.662 (0.432 to 1.013) p = 0.057	**Negative direction** **P = 0.057**
Ip, MedRxiv, 2020 – Inpatients (No) (40)	**USA**	**1914**	**598**	"This retrospective observational cohort study of 2512 hospitalized COVID-19 patients within a 13- hospital network did not find the empirical use of hydroxychloroquine with or without co-treatment with azithromycin to be associated with a reduction in mortality (adjusted HR, 0.99 for any hydroxychloroquine during hospitalization [95% CI, 0.80-1.22])."	**Negative direction** **P* = 0.93**
Ip, MedRxiv, 2020 – Outpatients (AHG reports being a study investigator for Genentech-Hoffman La Roche, during	**USA**	**97 (propensity score**	**970 (propensity score**	Table 1 Baseline characteristics and outcomes / Propensity-score-Matched patients (N=1077) / Death	**Negative direction** **p-value = 0.427**

the conduct of the study; research funding as study investigator from Acerta, AstraZeneca, Celgene, Kite Pharma, Elsevier's PracticeUpdate Oncology, Gilead) (41)		**matched patients)**	**matched patients)**	p-value = 0.427	
Mikami, J Gen Intern Med, 2020 (No) (42)	**USA**	**2077**	**743**	Table 3 Risk Factors Associated with In-Hospital Death Hydroxychloroquine use HR 0.53 (0.41–0.67), p < 0.001	**Negative direction** **P* = 6.6xE-07**
Roomi, J Med Internet Res, 2020 (No) (43)	**USA**	**144**	**32**	Table 3: HCQ regression analysis with the outcome Adjusted OR (95%CI) 1.6 (0.33-7.9) p = 0.54	**Positive direction** **P = 0.54**
Rosenberg, JAMA, 2020 – HCQ alone (Dr Dufort reported that her spouse has a Gilead Foundation-Focus HIV/HCV testing research grant.) (44)	**USA**	**271**	**221**	Table 3. Model-Adjusted Risk of In-Hospital Death, Cardiac Arrest, Arrhythmia / In-hospital death (hazard ratio) / Hydroxychloroquine alone vs neither drug HR 1.08 (0.63-1.85)	**Positive direction** **P* = 0.79**
Rosenberg, JAMA, 2020 – HCQ+AZ (Dr Dufort reported that her spouse has a Gilead Foundation-Focus HIV/HCV testing research grant.) (44)	**USA**	**735**	**221**	Table 3. Model-Adjusted Risk of In-Hospital Death, Cardiac Arrest, Arrhythmia / In-hospital death (hazard ratio) / Hydroxychloroquine + azithromycin vs neither drug HR 1.35 (0.76-2.40)	**Positive direction** **P* = 0.31**

Sbidian, MedRxiv, 2020 – HCQ alone (No) (45)	**France**	**623**	**3792**	Table 3. Primary and secondary outcomes according to study population and treatment group / HCQ alone vs. neither drug / AIPTW Estimate* (95%CI) / Whole population / Ratio in average treatment effect / 1.05 (0.77 to 1.33)	**Positive direction P* = 0.73**
Sbidian, MedRxiv, 2020 – HCQ+AZ (No) (45)	**France**	**227**	**3792**	Table 3. Primary and secondary outcomes according to study population and treatment group / HCQ plus AZI vs. neither drug / AIPTW Estimate* (95%CI) / Whole population / Ratio in average treatment effect / 1.40 (0.98 to 1.81)	**Positive direction P* = 0.031**
Singh, MedRxiv, 2020 (No) (46)	**USA**	**910 (propensity score matched patients)**	**910 (propensity score matched patients)**	Table 1: Comparison of patient characteristics and outcomes among hospitalized COVID-19 Hydroxychloroquine Treatment group and Control Group / Treatment Hydroxychloroquine vs Control (Matched Cohorts) / Mortality 30-Day / Relative risk (95%CI)	**Negative direction P = 0.72**

				0.95 (0.74-1.23) p = 0.72	
Sulaiman, MedRxiv, 2020 (No) (47)	**Saudi Arabia**	**1817**	**3724**	Adjusted OR “0.36 (0.16 - 0.8) 0.012”	**P = 0.012**

CQ: Chloroquine, HCQ: hydroxychloroquine, (H)CQ: chloroquine derivative (HCQ or CQ), OR: Odds ratio, HR: Hazard ratio, Positive direction : Ratio > 1 ((H)CQ associated with higher mortality, Negative direction : ratio < 1 : (H)CQ associated with lower mortality. In the software, the data entered were the number of patients with treatment, without treatment and the effect size data. *Altman DG, Bland JM. How to obtain the P value from a confidence interval. BMJ. 2011;343:d2304. doi:10.1136/bmj.d2304. Bold: data entered in the CMA software

Supplementary Table 3. Studies assessing the viral shedding outcome but excluded and reason for exclusion

Study	Reason
Gautret, Int J Antimicrob Agents, 2020 (48)	Included in Lagier, 2020
Mitja, Clin Infect Dis, 2020 (49)	"The viral load was provided in logarithmic scale; specimens with undetectable viral load at a given follow-up assessment were assigned a value of 3 log10 copies per mL (i.e., lower limit of detection) for the purpose of statistical analysis." As mentioned in our methods, we excluded studies that did not mention the proportion of positive. To our opinion, a negative PCR cannot be confused with a positive PCR with 3 log 10 copies DNA/mL.

Supplementary Table 4. Chloroquine derivatives and COVID19 Viral shedding – Data extracted (as of September 2020, 21)

Study (conflict of interest)	Country	N treated	N untreated	Data in the manuscript	Data entered in the software
BIG DATA STUDIES					
An, MedRxiv, 2020 – HCQ (No) (50)	South Korea	**20 (matched patients)**	**20 (matched patients)**	Table 3. Associations between hydroxychloroquine use and time to viral clearance and symptom duration in crude analysis, multivariable analysis, and propensity-score matching compare to standard supportive therapy. (Conservative therapy is the reference) / Time to viral clearance / Cox regression with matched population (n=20) ** HR 1.53 (0.83-2.94) p = 0.184	**Positive direction P = 0.184**
CLINICAL STUDIES					
Chen CP, MedRxiv, 2020 – HCQ – RCT (No) (51)	Taiwan	**21**	**12**	Table 2. Proportions of negative rRT-PCR assessments on day 14 and median times to negative rRT-PCR results after randomization in the multicenter, open-label, randomized controlled trial / Median time to negative# (Days, 95% CI) P-value*2	**Negative direction P = 0.40**

				#Time to negative = Event date or censored date – start day / *2 Log-rank test stratified by clinical syndromes 5 (1,9) vs 10 (2,12), p = 0.40	
Chen CP, MedRxiv, 2020 – HCQ – Retrospective study (No) (51)	Taiwan	**16**	**28**	"The median times (ranges) to undetected virus were 15 (6–31) days for the HCQ group and 14 (7–22) days for the control group (p = 0.37)"	**Positive direction** **P = 0.37**
Chen L, MedRxiv, 2020 – CQ (No) (52)	**China**	**18**	**12**	"Compared with the control group [median day: 7.0 (IQR: 3.0-10.0) days], the chloroquine group [median day: 2.5 (IQR: 2.0-3.8) days] (…) had significant decreases in the number of days required to reach RT-PCR negativity (P=0.006 (…) by Logrank (Mantel-Cox) test, respectively) (Figure 2b)."	**Negative direction** **P = 0.006**
Chen L, MedRxiv, 2020 – HCQ (No) (52)	**China**	**18**	**12**	"Compared with the control group [median day: 7.0 (IQR: 3.0-10.0) days], (…) the hydroxychloroquine group [median day: 2.0 (IQR: 2.0-3.5) days] had significant decreases in the number of days required to reach	**Negative direction** **P = 0.010**

				RT-PCR negativity ((…) P=0.010 by Logrank (Mantel-Cox) test, respectively) (Figure 2b)."	
Chen J, J Zheijang U, 2020 – HCQ – RCT (No) (53)	**China**	**15**	**15**	"On day 7, nucleic acid of throat swab was negative in 13 (86.7%) cases in the HCQ group and 14 (93.3%) cases in the control group (p > 0.05)."	**2/15 vs 1/15**
Huang, J Mol Cell Biol, 2020 – HCQ – RCT (No) (54)	**China**	**10**	**12**	"There were then steady increases in the number of patients turning negative, cumulating at Day 13 when all of the Chloroquine-treated patients became negative (Figure 1B, left panel; Supplementary Table S2). In comparison, patients in the Lopinavir/Ritonavir group only became SARS-CoV-2 negative after 3 days of dosing, and 11 out of 12 turned negative at Day 14."	**0/10 vs 1/12**
Huang, MedRxiv, 2020 – CQ – Prospective observational study (No) (55)	**China**	**197**	**176**	Table 2. Outcomes in the overall population with confirmed SARS-CoV-2 infection§. Patients with undetectable viral RNA by Day 10, N (%) 180/197 vs 101/176	**Proportion of positive (17/197 vs 75/176)**

Kamran, MedRxiv, 2020 – HCQ – RCT (No) (56)	**Pakistan**	**151**	**349**	Table-2. Assessment of Effect of HCQ on RT-PCR status of study population RT-PCR at day 7 / TREATMENT / 167/349 vs 97/151, p = 0.001 (NB: difference in PCR is most important around day 7, see Fig. 3 Lagier, TMAID, 2020)	**(proportion of positive PCR at day 7) 167/349 vs 97/151**
Kim, MedRxiv, 2020 – HCQ+AZ+Cefixime (No) (57)	**South Korea**	**22**	**40**	"The length of time to viral clearance, which was indicated by negative conversion on PCR after initiation of treatment, was significantly shorter with HQ plus antibiotics than with (…) conservative treatments (HR, 0.44; 95% CI, 0.25 to 0.78)."	**Negative direction** **P* = 0.0047**
Lagier, Travel Med Infect Dis, 2020 – HCQ+AZ (No) (26)	**France**	**3119**	**618**	Table 5 Age stratified multivariable analyses adjusted on comorbidities and severity of the disease addressing associations between treatment (HCQ-AZ ≥ 3 days) and clinical outcomes/viral shedding clearance (n = 3,737). Viral shedding persistence ≥ 10 daysf / All patients (n =	**Negative direction** **P* = 3.9E-07**

				3,737) / 10.6% vs 20.6%, HR 1.29 (1.17–1.42) p <0.0001	
Lecronier, Crit Care, 2020 – HCQ (No) (28)	**France**	**38**	**22**	Table 4 Virological findings on admission and on day 7 / Respiratory RT-PCR at day 7 / Positive RT-PCR, n (%) 19/26 vs 12/14 (positive / samples analyzed)	**19/26 vs 12/14**
Shabrawishi, MedRxiv, 2020 – HCQ/CQ (No) (58)	**Saudi Arabia**	**45**	**48**	"The primary endpoint of the study is achieving negative SARS-CoV-2 nasopharyngeal PCR within five days or less from the start of the intervention. Secondary endpoint was achieving negative sample within 12 days or less from the first positive PCR result." "In group A 73.3% (n= 33) achieved the primary endpoint and 84.4% (n= 38) achieved the secondary endpoint. Smaller percentage of patients 68.8 (n= 33) and 79.2% (n= 38) achieved the primary and secondary endpoints in group B."	**HCQ 33/45 vs 33/48**
Tang, MedRxiv, 2020 – HCQ – RCT (No) (59)	**China**	**75**	**75**	"The median time to negative	**Positive direction P = 0.34**

				conversion was also similar in the SOC plus HCQ group (8 days, 95%CI 5 to 10 days) with that in the SOC group (7 days, 95%CI 5 to 8 days) (Hazard ratio, 0.846; 95%CI, 0.58 to 1.23; p=0.34 by log–rank test) (Figure 2)	

CQ: Chloroquine, HCQ: hydroxychloroquine, (H)CQ: chloroquine derivative (HCQ or CQ), OR: Odds ratio, HR: Hazard ratio, Positive direction : Ratio > 1 ((H)CQ associated with higher mortality, Negative direction : ratio < 1 : (H)CQ associated with lower mortality. In the software, the data entered were the number of patients with treatment, without treatment and the effect size data. *Altman DG, Bland JM. How to obtain the P value from a confidence interval. BMJ. 2011;343:d2304. doi:10.1136/bmj.d2304. Bold: data entered in the CMA software.

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