Meta-analysis on chloroquine derivatives and COVID-19 mortality and viral shedding

October, 19, 2020 Update

SUPPLEMENTARY DATA

Changes since the last update (September 16, 2020) are in red

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. Importantly, manuscripts submitted to a peer-reviewed journal but not published online and whose submitted draft leaked on the internet were not 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 Final publication Horby et al., N Eng J Med, 2020 (8) https://www.nejm.org/doi/full/10.1056/NEJMoa2022926	Toxic doses (2400 mg fir the first 24 hours), PCR confirmation was not mandatory
Kelly, Br Pharmcol Soc, 2020 (9) 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 (10,11) 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 (12) 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 (13) https://www.medrxiv.org/content/ 10.1101/2020.08.14.20173369v1	HCQ initiation when patients deteriorated
Rivera, Cancer Discovery, 2020 (14) https://cancerdiscovery.aacrjournals.org/	Confounding by indication

content/early/2020/07/21/2159-8290.CD-20-0941	
Sanchez Alvarez, Nefrologia, 2020 (15) https://www.sciencedirect.com/science/ article/pii/S201325142030050X	Number of treated and untreated patients not provided
Singh, MedRxiv, 2020 (No) (16)	Diagnosis not confirmed by PCR "Occurred on or after Jan 20, 2020 ICD-10 Diagnosis codes U07.1: 2019-nCoV acute respiratory disease;U07.2 COVID-19 clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available; B34.2: Coronavirus Infection; J12.81: Pneumonia due to SARS-associated coronavirus; B97.29: Other coronavirus as the cause of diseases classified elsewhere Or LOINC Laboratory positive test result 94315-9 SARS coronavirus 2 E gene; 94533-7 SARS coronavirus 2 N gene in Respiratory specimen; 94500-6 SARS coronavirus 2 RNA in Respiratory specimen; 94534-5 SARS coronavirus 2 RdRp gene in Respiratory specimen; 94506-3 SARS coronavirus 2 IgM Ab in Serum or Plasma; 94505-5 SARS coronavirus 2 IgG Ab in Serum or Plasma; 41458-1 SARS coronavirus RNA; 94309-2 SARS coronavirus 2 RNA"
Skipper, Annals of Internal Medicine, 2020 (17) 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.
Soto-Becerra, MedRxiv, 2020 (18) https://www.medrxiv.org/content/ 10.1101/2020.10.06.20208066v2	The severity of the disease is not assessed (no severity score). A "confounding by indication" could not be ruled out. Patients who received hydroxychloroquine after 48 hours of hospitalization were assigned to the control group.
Synolaki, MedRxiv, 2020 (19) 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 – HCQ (No) (20)	**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) (21)	**Iran**	**427**	**32**	Table 4. Therapies and outcomes. P = 0.028	**Negative direction P = 0.028**
Alberici, Kidney International, 2020 – HCQ (No) (22)	**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) (23)	**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) (24)	**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) (24)	**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) (25)	**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) (25)	**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) (26)	**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) (27)	**France**	**20**	**34**	"One patient, a man of 82-year-old without comorbidities in the NST group died suddenly;"	**0/20 vs 1/34**
Heberto, IJC Heart & Vasc, 2020 HCQ+AZ (No) (28)	**Mexico**	**139**	**115**	Table 4 Cox regression analysis identifying predictors of mechanical ventilation and mortality risk. HCQ/Azithromycin OR 0.357 95% CI 0.133-0.955 p = 0.040	**Negative direction** **P = 0.040**
Heras, Researchsquare, 2020 – HCQ+AZ (No) (29)	**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) (29)	**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 – HCQ+AZ (No) (30)	**France**	**503**	**199**	Table 5 Age stratified multivariable analyses adjusted on comorbidities and severity of	**Negative direction** **P = 0.003**

				the disease addressing associations between treatment (HCQ-AZ ≥ 3 days) and clinical outcomes/viral shedding clearance (n = 3,737). Weighted Cox regression on Unmatched sample (n = 702) Hazard ratio 0.49 (0.31–0.79), p = 0.0030	
Lauriola, Clinical Transl Sci, 2020 – HCQ alone (No) (31)	**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) (31)	**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 - HCQ (No) (32)	**France**	**38**	**22**	Table 2 Primary and secondary outcomes - 28-day mortality, n (%) standard of care 9/22 vs	**9/38 vs 9/22**

				Lopinavir/ritonavir 7/20 vs hydroxychloroquine 9/38, p = 0.35	
Ly, IHU preprints, 2020 (No) (33)	**France**	**116**	**110**	Table 3. Associations between multiple factors and SARS-CoV-2 death among 226 infected elderly residents (univariate and multivariate analysis) / HCQ/AZ treatment for at least 3 days (226) / Multivariate 0.39 [0.17-0.89] 0.026	**Negative direction P = 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 /) (34)	**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) (35)	**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) (36)	**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 /) (37)	**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)	**Negative direction** **P = 0.0001**

				p<0.0001	
Scholz, Preprints, 2020 (No) (38)	**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**
Serrano Domingo, Ann Oncol, 2020 HCQ+AZ (No) (39)	**Spain**	**14**	**8**	"There seems to be a trend towards lower mortality among patients who received treatment with the combination of hydroxychloroquine and azithromycin than among those who did not (6/14 vs 6/8; P.0.145)."	**Negative direction P = 0.145**
Ulrich, Open Forum Infect Dis, 2020 (No) (40)	**USA**	**67**	**61**	7/67 (10.4%) vs 6/61 (9.8%) p = 1.000	**Null direction P = 1.0**
Yu, Sci China Life Sci, 2020 (No) (41)	**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					
Ayerbe, Intern Emerg Med, 2020 – HCQ (No) (42)	**Spain**	**1857**	**162**	Table 2 Association between HCQ and mortality – Mortality. Odds ratio (95% CI) (Model 4) 0.39 (0.24-0.64)	**Negative direction P* = 0.000148**

Bernaola, MedRxiv, 2020 (No) (43)	**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) (44)	**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) (45)	**Italy**	**2634**	**817**	Table 2 Incidence rates and hazard ratios for death in COVID-19 patients, according to hydroxychloroquine use Propensity score analysis, inverse probability weighting** (primary analysis) HR 0.70 (0.59 to 0.84)	**Negative direction P* = 8.66xE-05**
Gonzalez, MedRxiv, 2020 (No) (46)	**Spain**	**8448**	**1169**	Table 4. Multivariate analysis of mortality. The effect of each factor is	**Negative direction P = 0.057**

				expressed as an Adjusted Odds Ratios (CI 95%). Hydroxychloroquine Adjusted OR 0.662 (0.432 to 1.013) p = 0.057	
Ip, MedRxiv, 2020 – Inpatients (No) (47) Final publication : Ip, PlosOne, 2020 (48)	**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 the conduct of the study; research funding as study investigator from Acerta, AstraZeneca, Celgene, Kite Pharma, Elsevier's PracticeUpdate Oncology, Gilead) (49)	**USA**	**97 (propensity score matched patients)**	**970 (propensity score matched patients)**	Table 1 Baseline characteristics and outcomes / Propensity-score-Matched patients (N=1077) / Death p-value = 0.427	**Negative direction** **p-value = 0.427**

Mikami, J Gen Intern Med, 2020 (No) (50)	**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**
Nachega, Am J Trop Med Hyg, 2020 – HCQ+AZ (No) (51)	**Democratic Republic of the Congo**	**630**	**96**	TABLE 3 Cox regression of factors associated with hazard of death (N = 766) Adjusted hazards ratio (95% CI)* Chloroquine/azithromycin–based Treatment aHR 0.26 (95%CI 0.16-0.42) p < 0.001	**Negative direction** **P* = 7.7x10-8**
Roomi, J Med Internet Res, 2020 (No) (52)	**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.) (53)	**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.) (53)	**USA**	**735**	**221**	Table 3. Model-Adjusted Risk of In-Hospital Death, Cardiac Arrest, Arrhythmia / In-hospital death (hazard ratio) /	**Positive direction** **P* = 0.31**

				Hydroxychloroquine + azithromycin vs neither drug HR 1.35 (0.76-2.40)	
Sbidian, MedRxiv, 2020 – HCQ alone (No) (54)	**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) (54)	**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**
Sulaiman, MedRxiv, 2020 (No) (55)	**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 (56)	Included in Lagier, 2020
Mitja, Clin Infect Dis, 2020 (57)	"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) (58)	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) (59)	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) (59)	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) (60)	**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) (60)	**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) (61)	**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) (62)	**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) (63) Final publication: Huang, Natl Sci rev, 2020 (64)	**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) (65)	**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) (66)	**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) (30)	**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) (32)	**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) (67)	**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) (68)	**China**	**75**	**75**	"The median time to negative	**Positive direction P = 0.34**

Final publication : Tang, BMJ, 2020 (69)				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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