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Predictive factors of clinical assays on hydroxychloroquine for COVID-19 mortality during the first year of the pandemic: a meta-synthesis

SUPPLEMENTARY DATA

Supplementary methods:

Global strategy

In the context of a global crisis of trust in medical literature triggered by a retracted article published in the Lancet (1), we performed a critical reading of scientific publications on the clinical efficacy of chloroquine derivatives and remdesivir against Covid-19 since March 2020 (2). We primarily focused on mortality and considered all studies with Covid-19 patients treated or not treated by hydroxychloroquine (HCQ) or remdesivir with at least 1 death. We began by looking at each article and identifying anomalies that we felt were unacceptable or to be avoided from a medical point of view (3-7). Gradually this led us to identify essential or recommended judgement criteria which were gathered in a checklist. In November 2020, we stopped this checklist, which is provided here (Table 1).

We then comprehensively reviewed all the publications and preprints with this checklist and described for each criterion the triggering study, and all the studies that did not meet them. We then analyzed all the articles using unsupervised approach. Finally, we performed a comparative meta-analysis, as described previously (2), comparing studies that met or did not meet each criterion. When 2 studies studied common patients or the same cohort, both of them could be analyzed for criteria identification but only the most recent one, with the largest number of patients, published versus preprint or including the most recommended criteria identified here were included in the quantitative meta-analysis to assess HCQ efficacy.

Inclusions of studies: Search strategy

The keywords "hydroxychloroquine", "HCQ", "chloroquine", "coronavirus", "COVID-19" and "SARS-Cov-2", "remdesivir" were used in the PubMed, Google Scholar and Google search engines for studies published in English (research updated on November, 11, 2020). An online search was also performed using the website https://c19study.com/. The following outcome was considered; death, therefore studies without any death were not eligible. Preprints were also included. When preprints were subsequently published, final publication and preprints were compared. We reviewed studies evaluating the effects of chloroquine derivatives against SARS-CoV-2 in groups of COVID-19 patients compared to control groups of patients who did not receive chloroquine derivatives.

Articles published in peer-reviewed journals, preprints and articles available on the internet, even when not published on official websites, were included. Manuscripts submitted to a peer-reviewed journal but not published online and whose submitted draft leaked on the internet were not included. Only studies comparing a group of COVID-19 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 delays of treatment were not eligible. Studies analyzing safety, efficacy as a prevention, and data provided as a webpage without any article format (such as a tweet), were also not eligible.

Identification of characteristics and criteria

The criteria are summarized in Table 1. Some of these criteria have already been identified in a previous work (3,8) and have been completed as we observed critical pitfalls in studies assessed for the present work. A criterion was not fulfilled if it was mentioned but not fulfilled and/or if it was not mentioned.

In the retracted article (1) which triggered the scandal, we identified several quality criteria not fulfilled; *absence of private company computing data*, *centers and doctors who take care of patients are identified*, *the therapeutic protocol is detailed (standard care, evaluation of contra-*

indications, dosage and duration) and *at least one main author is a clinical expert-in-the-field (affiliated to an infectious disease, internal medicine or a pneumology unit)*. Indeed, a private data computing company (Surgisphere) collected data, centers and doctors were not identified, therapeutic protocol was not mentioned, and authors were not affiliated to an infectious disease, internal medicine or pneumology units but to biomedical, heart and vascular units.

In other studies, we identified the following medical quality criteria;
Potential conflict of interest such as a study reporting an increased mortality with HCQ compared with standard-of-care funded by the company marketing remdesivir (9), with a design strikingly similar to the retracted article (1). Potential conflict of interest was defined when the name of a company marketing remdesivir was mentioned in the manuscript as a funder or as a conflict of interest with at least 1 author or 1 investigator either declared or found on transparency websites (transparence.sante.gouv.fr, eurosfordocs, dollarsfordocs) but not declared. A non-compensated consulting was not considered a potential conflict of interest (10).

Absence of undeclared funding and conflict of interest: an author disclosed a financial relationship with a company marketing remdesivir in 2019 (https://www.astmh.org/ASTMH/media/2019-Annual-Meeting/ASTMH-2019-Speaker-Disclosure-Statement.pdf), but not in his two studies reporting an absence of effect of HCQ to prevent (11) or treat Covid-19 (12).

Patients without confirmation of diagnosis by a microbiological test are excluded: The same authors not declaring any conflict of interest confirmed cases with a microbiological test in only 18% (11) or 34% of cases (12). Laboratory confirmation is essential as clinical diagnosis is not sufficient because many respiratory viruses circulate at the same time (13).

The treatment is not toxic (not overdosed or used in contraindicated patients): A study (14) used 1.5 times the loading dose of chloroquine-sensitive malaria (www.cdc.gov), and 4 times the usual dosage in other acute infectious diseases, such as liver amebiasis (15).

Patients in the no-treatment group are not treated with the experimental treatment or with any other treatment that the treated group did not have. This was observed in a study in which treated patients received only HCQ but 30% of untreated patients received azithromycin (16).

Confounding role of previous health status (at least age) is ruled out. This was not the case in a paper (17) where patients were older, but no attempt was done to control this confounding.

Confounding role of disease severity (at least oxygen status) is ruled out. Strikingly, in a study (9), twice as many patients were intubated in the HCQ group than in the non-HCQ group (24.9% vs 12.2%) and this was not controlled. We already commented on this (5). Other errors were observed but their effect could not be adequately quantified by quantitative meta-analysis and Q-value.

Conclusions neglecting a non-significant decrease or increase in mortality of 25% or more (18,19). In this case, indeed, there is a difference but as the study does not have the power to confirm it significantly, it could be due to chance or to the poor design. Typically, these studies should be used for meta-analysis that will confer the power to confirm or not the significance of the difference.

Clinical relevance should be evaluated (19). Strikingly, the 28-day mortality was halved in a French RCT suspended and closed after the publication of Mehra et al., (1). The difference was clinically relevant since the number of patients needed to prevent 1 death was 25 (mortality at day 28 of 4.8% in HCQ and 8.9% in untreated).

Conclusions neglecting an unexpected relevant result: A study found no death in patients treated by the combination therapy associating hydroxychloroquine and azithromycin (20), but this was not tested nor discussed.

The main outcome is objective, independent of human subjectivity and context and did not change during study: In an observational study, the main outcome was death and/or transfer to intensive care unit (ICU) (21) but ICU transfer is highly subjective and depends on the physician and the number of available ICU beds. Death is only mentioned in the supplementary data without methods to control confounding with previous health status or severity while treated patients were much more severe at baseline. In an RCT (22), the main outcome changed from "difference in clinical status" to "time to recovery" during the study.

Identified articles: preprints, published articles, censorship during editing: Overall, 61 studies were evaluated. For HCQ/CQ, 56 studies (with at least 1 death) were identified (Supplementary File 1) corresponding to 23 preprints (14 without publication in a peer-reviewed journal and 9 preprints subsequently published in a journal), and 33 studies published in a journal without previous preprint. A preprint study (23) and a study published in a journal (24) from different authors analyzed the same Spanish cohort. For remdesivir, only 6 studies were found including 3 preprints and 4 peer-reviewed publications (10, 22,25-29). One study was common for HCQ and remdesivir and was published both as a preprint (25) and a peer-reviewed publication (26). We observed discordances between preprints and final manuscripts. Data evidencing a favorable effect of HCQ (alleviations of symptoms, greater reduction of CRP, more rapid recovery from lymphopenia) were mentioned in the preprint (30) but removed in the final published version (31). This deletion was requested by the editor of the journal. Conversely, Magagnoli improved quality between preprint (16) and final publication (32) including a subgroup analysis by severity before treatment. The 56 studies on HCQ/CQ came from the USA (n=16), France (n=9), Spain (n=6), Italy (n=4), Iran, Ireland (n=2 each), and Andorra, Belgium, Brazil, China, Congo, Egypt, Greece, India, Mexico, the Netherlands, Peru, Saudi Arabia, Turkey and the United Kingdom (n=1 each). Three studies involved more than 1 country. Strikingly, only 1 included study came from China while several comparative studies have been reported from this country without any death (30,31,33-37). For remdesivir, 3 studies were performed in the USA, 1 in China, 1 in Poland and 1 was multinational. Among all 61 evaluated studies, 49 were observational including 24 Big data studies. We found 12 RCTs including 9 megatrials. Forty-three studies were multicentric and 18 were monocentric. For 6 studies, data for death analysis were not sufficient for quantitative meta-analysis (sample size in each group, with number of death or summary result for death not provided).

Funding, conflict of interest of studies evaluating HCQ or remdesivir on Covid-19 mortality

We considered it to be a conflict of interest when the study was funded by Gilead directly (remdesivir) or indirectly (9) or when at least 1 author received fees from Gilead and declared it or did not declare it.

Studies funded by pharmaceutical industries

We found that 4 studies were funded by pharmaceutical industries. Studies by Fried et al. (9), Goldman et al., (38) and Spinner et al., (29) were funded by Gilead who market remdesivir. Cavalcanti (39) was funded by the first Brazilian big pharma industrial (EMS Pharma) but we found no link about this industry regarding a conflict of interest so this study was considered "without conflict of interest". These 4 studies were published in the journals with the highest impact factors in medicine and infectious diseases. In the RCT reported by Goldman et al., (38) comparing two durations of remdesivir (without placebo), 109/397 (27.4%) patients were treated with HCQ and mentioned in supplementary data but were not analyzed. In this RCT, hydroxychloroquine was associated with lower death rate (9 versus 12%).

Declared conflict of interests

In Beigel et al., (22), employees of Gilead Sciences participated in discussions about protocol development and in weekly protocol team calls. Seven authors declared a conflict of interests with Gilead. In Flisiak et al. (28), 6/22 authors received personal fees from Gilead and this was declared.

Undeclared conflict of interests

In Geleris et al., (21), an author received at least 9,413 $ for consulting from Gilead Sciences inc on Jan 31, 2018 (https://projects.propublica.org/docdollars/). Mahevas et al., (40) declared no funding received nor conflict of interest in their study but the competing interests were not fully declared in the original publication so that an erratum was published (40,41) with an updated and expanded conflict of interest statement with almost all authors receiving personal fees from pharmaceutical industries. Another author of the same work, with initially undeclared conflict of interest in this publication, declared a conflict of interest in some publications on HCQ and remdesivir (42) but not in others (43-46).

An author (D. Boulware) disclosed a financial relationship with Gilead in 2019 (https://www.astmh.org/ASTMH/media/2019-Annual-Meeting/ASTMH-2019-Speaker-Disclosure-Statement.pdf), but not in his two studies reporting an absence of effect of hydroxychloroquine to prevent (11) or treat Covid-19 (12).

In the WHO Solidarity trial (25,26) published as a preprint in MedRxiv, no author declared any conflict of interest while in supplementary data, it appeared that several participants, especially investigators who included patients in the trials, had received fees from Gilead. Moreover, 4 authors finally reported personal fees from Gilead in the final publication (26) whereas this was not reported

in the preprint where it could be read "Competing Interest Statement: The authors have declared no competing interest' (25).

Possible conflict of interests

In two articles, we found several conflicts of interests between authors and several pharmaceutical industries (47,48), however, we did not find Gilead in these industries. It is however, possible that unreported conflicts of interests exist between other firms and a possible efficacy of hydroxychloroquine.

Besides for-profit private data computing companies, we found two Big Data studies performed with the US Department of Veterans affairs associated with HCQ inefficacy (27,49-50) and remdesivir efficacy (27). We also identified a RCT associated with HCQ inefficacy and remdesivir efficacy with one author funded by US Veterans affairs (51). Strikingly, Gilead supports veterans through the Gilead Veterans Engagement Team (https://www.gilead.com/careers/inclusion-and-diversity) and has intricated relationships with the US Department of Veterans affairs since anti-HCV sofosbuvir development (https://www.military.com/daily-news/2016/02/05/former-va-scientist-responds-to-lawmakers-suspicions-drug-sale.html). Furthermore, Gilead provided remdesivir to US army at no cost (https://www.militarytimes.com/news/your-military/2020/03/10/army-signs-agreement-with-drug-giant-gilead-on-experimental-covid-19-treatment/). Finally, a thorough investigation may decipher potential conflict of interest when the same investors finance both the company whose authors are employees and the company that markets the remdesivir (52).

For-profit private data computing companies and Big Data studies

We found 3 "Big Data" studies with a possible shell company (private data computing company); (i) Surgisphere was a private data computing company in a study subsequently retracted (1). We did not succeed in identifying the main actionnaires of this company despite thorough internet research (https://www.prnewswire.com/news-releases/ihfs-global-healthcare-quality-award-recognizes-surgisphere-executive-sapan-desai-md-300637851.html); (ii) Target Pharma-Solutions in a study published in Clinical Infectious Diseases with funding for initial data acquisition provided by Gilead (9), and (iii) TriNetX in a preprint (49) and in a published paper (50). Target PharmaSolutions is a for-profit company with a total funding amount of $637K with 5 members and 3 investors funded by the first author of the publication [M. Fried (https://www.crunchbase.com/organization/target-pharmasolutions) (9)]. TriNetX (49,50) is an initiative of the West Virginia Clinical and Translational Science Institute (https://www.wvctsi.org/programs/epidemiology-biostatistics/ trinetx/), with active link with Sanofi (https://trinetx.com/sanofi/), Merck, Itochu, Novartis, and Pfizer (https://www.outsourcing-pharma.com/Article/2018/01/16/Sanofi-partners-with-TriNetX-to-speed-drug-development-timelines & https://www.frenchweb.fr/trinetx-leve-40-millions-de-dollars-pour-exporter-ses-solutions-doptimisation-des-essais-cliniques-en-europe/351399).

Studies that did not mention treatment details

Contraindications were not mentioned in several Big Data studies (23). In the Big Data study by Sbidian et al., (53) including 39 hospitals in Paris, it is not possible to know the posology nor the duration. The suggested HCQ regimen is mentioned "loading dose of 600 mg on day 1, followed by 400 mg daily for 9 additional days. AZI at a dose of 500 mg on day 1 and then 250 mg daily for 4 more days in combination with HCQ was an additional suggested therapeutic option. Prescription of HCQ or HCQ together with AZI was at the discretion of the physicians." In this multicentric big data study, the absence of data on treatment and the absence of standardized protocol may prevent any conclusion.

Studies without control for initial disease severity

Eight studies with treated patients more severe at baseline

We found 8 studies in which severity was not controlled for and with treated patients more severe than untreated patients. Strikingly, in the study by Fried et al., (9), whose initial data acquisition was provided by Gilead, HCQ-treated patients had more severe disease (more frequent pneumonia) and the authors reported an increased mortality in the HCQ group without adjusting for any confounding. In Geleris et al., (21) published in the NEJM, the use of propensity score was not sufficient and after matching, the treated group still had a 20% lower PaO2/FiO2 ratio, a 40% higher ferritin, and an 18% higher CRP than the untreated group. In the study by Ip et al., (47) HCQ-treated patients were almost 2 times more likely to have a SaO2 < 94% (49% vs 30%, $p < 0.05$), and the propensity score model did not include this parameter while age, comorbidities and "log ferritin" were

included in the model. In Kelly et al., study (54), HCQ-treated patients had significantly higher CRP, FiO2 requirement and clinical scale at day 0 and there was no attempt to control this confounding. Magagnoli et al., (16,32) reported a propensity score analysis without mentioning covariates included in the model. Because treated patients were much more severe (lymphopenia twice as common in the treated group (25%) than in the untreated group (14%)), it was not possible to rule out a confounding role of severity. McGrail (17) reported that treated patients were older and more severe but did not attempt to control these confoundings. Finally, in the study by Peters et al., (55) treatment was started when there was an increase in respiratory rate or use of supplemental oxygen. This implied an uncontrollable confounding by indication bias. This "confounding by indication" bias seems associated with Big Data as we also found that severity was not adequately adjusted for in the study of the Covid-19 cancer consortium (matched data presented in Supplemental Table S5 of Rivera et al., (48): 93% moderate-severe in the HCQ group versus 80% in the untreated group). A conflict of interest was found for 3 of these studies (9,16,21,32) and highly suspected for 2 of them (47,48).

We did not find any study in which the treated patients were less severe than the untreated ones.

Studies in which difference of severity between treated and untreated could not be assessed

We found 16 studies in which a difference in severity between treated and untreated was not evidenced but could not be ruled out. Alamdari et al., (56) reported that expired patients presented more frequently with shortness of breath at admission and were less frequently treated, however effect of treatment was not controlled for initial severity. In Alberici et al., study (18), HCQ was associated with an important protective effect against death (OR = 0.44, p > 0.05) but HCQ was not included in multivariate analyses because p-value was not < 0.5. Indeed, only the statistically-significant predictors at univariate analysis were entered into a multivariate model. Bhandari et al. (57) reported, among asymptomatic patients at inclusion, 1 death/39 in the HCQ group versus 1/32 in the control one, however, oximetry was not provided in any of the two groups. As hypoxia could be asymptomatic (58), a difference in initial severity could not be ruled out. In the same study (57), asymptomatic patients were treated with HCQ or no treatment, mildly ill patients were treated with HCQ, severely ill with HCQ-AZ and critically ill with Lopinavir+ritonavir so that it was not possible to control for the role of disease severity. Calik Basaran et al., (59) reported a shorter length of hospitalization in HCQ-AZ but severity between groups was different at baseline and exposition of the 4 dead people (treated or untreated) was not provided. Derwand et al., (60) provided no information on the control population. Heberto et al., (61) reported a significantly decreased mortality in multivariate analysis but potential predictors included in the model were not provided, notably because myocardial injury but not death was the main outcome. Goldman et al., (38) found a mortality decrease with HCQ but did not analyze it because it was not the main outcome as the study was designed to assess remdesivir. Guerin et al., (62) performed a case-control sub-analysis matched for age, sex, and body mass index but not severity while some patients were severe (respiratory rate ranging from 12 to 50). Some studies reporting multivariate analyses did not mention the covariates included in the models, so a role of severity could not be excluded (62). Pinato et al., (63) made no mention of disease severity or oxygen requirements. In Roomi et al., (64), age was not different and controlled for in multivariate analyses, and the initial disease severity was not assessed and not included in multivariate analysis. Serrano et al., (65) in their abstract did not mention baseline characteristics and did not attempt to control for age or severity. In Singh et al., (49), previous health status and comorbidities were included for matching but disease severity was not considered in the propensity matching. Skipper et al., (12) in their internet-based RCT assessed "shortness of breath" but did not assess oxygen status (oximetry) at baseline. Soto-Beccera et al., (66) developed a complex model including several comorbidities and "pneumonia diagnosed within 48 hours of admission" but not oxygen status. Because we treated more than 30,000 patients in our center (as of December 2021), it is clear that pneumonia could be minimal, intermediate or severe with a very different risk of complications between minimal (<10% lung volume) and severe (>50%) involvement (67,68). Furthermore, since hypoxia is frequently asymptomatic (58), oxygen status could not rely on interview but required objective measurement. Sulaiman et al., (69) performed multivariate analysis including age, gender and comorbidities but disease severity was not controlled for. Synolaki et al., (70) did not analyze confounding for treatment as it was not the main topic of the paper.

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Supplementary Table 1: Comparative meta-analysis according to quality criteria identified in the present study

	Q-value	p-value of Q-value	Summary effect of studies fulfilling this criterion				Summary effect of studies not fulfilling this criterion			
			number of comparisons	OR	95% CI	p-value	number of comparisons	OR	95% CI	p-value
Absence of private data computing company	73.1	<.0001	56	0.81	0.74 - 0.89	<.0001	6	1.28	1.23 - 0.34	< .0001
Potential conflict of interest	39.3	< .0001	43	0.75	0.66 - 0.83	< .0001	19	1.15	1.07 - 1.23	0.0001
Detailed therapeutic protocol	28.5	< .0001	25	0.68	0.59 – 0.78	< .0001	37	1.04	0.96 – 1.12	0.34
Centers and doctors who take care of patients are identified	27.2	< .0001	41	0.70	0.61 - 0.80	< .0001	21	1.09	0.99 - 1.21	0.07
An author clinical expert-in-the-field*	21.0	< .0001	29	0.71	0.61 – 0.81	< .0001	25	1.06	0.96 – 1.16	0.25
Clinical study (Not a 'Big Data' study based on electronic medical files)	14.5	0.0001	34	0.66	0.55 – 0.79	< .0001	28	0.99	0.89 – 1.09	0.83
Nontoxic treatment (dose, use in contraindicated patients)	13.9	0.0002	58	0.85	0.78 - 0.93	0.0008	4	1.09	0.998 - 1.20	0.06
Observational versus interventional (RCTs)	12.5	0.0004	52	0.85	0.77 – 0.94	0.001	10	1.07	0.98 – 1.17	0.11
Monocentric versus multicentric	12.3	0.0004	18	0.55	0.41 – 0.73	< .0001	44	0.95	0.87 – 1.03	0.22
Not a megatrial	11.9	0.001	55	0.86	0.78 – 0.94	0.001	7	1.07	0.98 – 1.17	0.11
Control group without another specific treatment effective on SARS-Cov-2 (other treatment, HCQ or AZ)	11.4	0.001	60	0.85	0.78 - 0.93	0.001	2	1.33	1.05 - 1.70	0.02
Number of events, total treated untreated known	7.66	0.006	49	0.94	0.86 - 1.03	0.18	13	0.67	0.54 - 0.83	0.0004
Treatment monitoring	7.43	0.006	19	0.70	0.59 – 0.84	0.0001	43	0.93	0.85 – 1.03	0.16
Funding is mentioned, absence undeclared COI	7.11	0.008	55	0.86	0.78 - 0.94	0.001	7	1.07	0.93 - 1.23	0.32
Control for severity (at least oxygen)	6.62	0.01	39	0.80	0.72 - 0.90	0.0001	23	1.02	0.88 - 1.18	0.79
Absence of mixed stages of the disease	6.52	0.01	39	0.79	0.70 – 0.89	0.0001	23	0.98	0.87 – 1.10	0.72
Detailed Standard of Care (SoC)	6.03	0.01	7	0.60	0.45 – 0.82	0.001	55	0.90	0.82 – 0.986	0.023
Diagnosis formally confirmed (PCR or serology-based diagnosis)	4.98	0.026	48	0.84	0.76 - 0.93	0.001	14	1.04	0.89 - 1.21	0.64

Conclusions do not neglect a 25% difference in mortality risk	1.51	0.22	51	0.87	0.79 – 0.96	0.004	11	0.98	0.83 – 1.14	0.76
Unexpected findings reported	0.86	0.35	56	0.86	0.78 – 0.94	0.001	6	0.998	0.74 – 1.35	0.991
Objective outcome	0.23	0.63	56	0.87	0.79 – 0.95	0.002	6	0.90	0.80 – 1.002	0.053
Control for health status (at least age)	0.047	0.83	55	0.87	0.79 - 0.95	0.002	7	0.82	0.48 - 1.39	0.45

Random effect model, 62 comparisons. *For 8 comparisons, this could not be determined.

Supplementary Table 2: Criteria identified through errors and mistakes in analysis of studies assessing HCQ and remdesivir for Covid-19

Criteria	Explanation	PRISMA Checklist	STROBE Checklist	CONSORT Checklist
Potential sources of bias	In usual checklists, potential sources of bias are mentioned but not identified. In the context of Covid-19, the major sources of biases identified in the present study were conflict of interest and lack of clinical expertise	No	Item 9: Describe any efforts to address potential sources of bias *These sources of bias are not clearly identified. Conflict of interest and lack of clinical expertise not considered as potential sources of bias*	No
Conflict of interest		Item 27: Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Item 22: Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Item 25: Sources of funding and other support (such as supply of drugs), role of funders
Private data computing company	Collecting/aggregating data by for-profit companies should be avoided. The financial links of such companies (shareholders) should be known	Not mentioned	Not mentioned	Not mentioned
Centers and doctors identified	Centers and doctors recruiting patient should be known	Not mentioned	Item 5: Setting Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Item 4b: Settings and locations where the data were collected Item 10. Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions?
Undeclared funding/conflict of interest	When investigating the funding of the study and conflicts of interest of each author[1], no undeclared/indirect funding or conflict of interest should be found	Research of funding is required but not research of conflict of interest	Research of funding is required but not research of conflict of interest	Research of funding is required but not research of conflict of interest

Potential conflict of interest	Study is not funded, and authors have not received fees from one or several pharmaceutical industries with a direct or indirect[2] conflict of interest with the results of the study	Not mentioned – PRISMA checklist does not mention conflict of interest of eligible studies.	Funding but not conflict of interest is considered.	Funding but not conflict of interest is considered.
Clinical expertise				
At least one of the authors is a clinical expert-in-the-field	For a viral respiratory infection such as Covid-19, at least 1 author is affiliated to an infectious disease, internal medicine or a pneumology unit. Biomedical, public health specialists are not clinical experts as far as they do not care for patients	Not mentioned	Not mentioned	Not mentioned
Diagnosis is confirmed by a laboratory test	Patients without a laboratory test are excluded. Diagnosis should not rely on clinical or radiological evidence only	Not mentioned	Item 6: Participants Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Item 7. Give diagnosis criteria, if applicable *No mention of a laboratory confirmation test*	Not mentioned
Detailed therapeutic protocol	A detailed therapeutic protocol is provided allowing a medical doctor expert-in-the-field to reproduce it, considering most common contraindications, precautions for use and monitoring.	Not mentioned	Not mentioned	Item 5: The interventions for each group are described with sufficient details to allow replication, including how and when they were actually administered. *No mention of contraindications, precautions of use and monitoring*
Treatment is not toxic	Dose is usual, not in the overdose range and follows commonly-used doses with this drug. Drug is not used in patients with contraindications	Not mentioned	Not mentioned	Not mentioned

A specific treatment effective on the microbe is not given to controls	Other drugs potentially effective on the microbe are known by the clinical expert. They should not be given to the untreated patients	Not mentioned	Not mentioned	Not mentioned
Role of previous health status is ruled out	A difference in previous health status between treated and untreated should not interfere with outcome (typically a difference of age or mortality). Combined Charlson score frequently used in this context.	Not mentioned	Item 7: Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Item 14: Give characteristics of study participants (e. g. demographic, clinical, social) and information on exposures and potential confounders *Control for previous health status (at least age) not required*	Item 15: A table showing baseline demographic and clinical characteristics for each group
Role of disease severity is ruled out	A difference in disease severity between treated and untreated should not interfere with outcome (typically a difference of vital parameters). NEWS score frequently used in this context.	Not mentioned	Item 7: Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Item 14: Give characteristics of study participants (e. g. demographic, clinical, social) and information on exposures and potential confounders *Control for disease severity (at least the relevant vital parameters) not required*	Item 15: A table showing baseline demographic and clinical characteristics for each group
A 25% lower mortality should not be neglected	Authors should not conclude an absence of effect when risk of mortality is decreased of more than 25%	Not mentioned	Not mentioned	Not mentioned
Clinical relevance should be evaluated	When a difference is observed and regardless of significance, the number	Not mentioned	Item 16(c). If relevant, consider translating	Item 17(b). For binary outcomes, presentation

	needed to treat (NNT) to prevent an event in the specified risk group should be reported. Assessment of clinical relevance may also include the years of life lost (YLL), years lived with disability (YLD) and disability adjusted live years (DALY)		estimates of relative risk into absolute risk for a meaningful time period	of both absolute and relative effect sizes is recommended
An unexpected clinically relevant finding should not be neglected	Authors should report unexpected finding for instance a very different effect size in a subgroup	Item 16: Additional analyses. Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not mentioned	Item 12b: Methods for additional analyses, such as subgroup analyses and adjusted analyses Item 18. Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Methodology				
Design of the study (RCT/observational) is mentioned	Design of the study should be mentioned	Design of the study should be mentioned	Item 4: Study design. Present key elements of study design early in the paper	Item 1a: Identification as a randomized trial in the title
Big Data studies are identified	It the data are analyzed by data scientists with electronic medical files without connection to the medical doctors who take care of patients, this should be mentioned	Not mentioned	Not mentioned	Not mentioned
Mono or multicentric design is known	This is naturally clarified when centers and doctors are known. If the study is an RCT with several recruiting centers, it should be identified as a megatrial associated with specific risks of bias (Simpson's paradox). Effect should be reported for each center	Not mentioned	Not mentioned	Not mentioned
Number of events and sample size of each group in each center are provided	This improves verifiability but is not sufficient *per se* to prevent other biases	Not mentioned	Not mentioned	For each primary and secondary outcome, results for each group, and the estimated

				effect size and its precision (such as 95% confidence interval) *No mention of the center*
In multicentric studies, adjusted effect is reported in each center	This prevents the Simpson's paradox	Simpson's paradox neglected	Simpson's paradox neglected	Simpson's paradox neglected

[1]For instance using governmental (https://www.transparence.sante.gouv.fr), or non-governmental transparency websites (https://projects.propublica.org/docdollars/, https://www.eurosfordocs.fr/), [2]A direct conflict of interest is found when the drug tested is sold by the pharmaceutical company which funded the study and/or paid fees to one or several authors, an indirect conflict of interest is defined when the drug tested is in the same niche and in competition with a drug (or pharmaceutical product (i.e. a vaccine)) sold or developed by the pharmaceutical company which funded the study and/or paid fees to one or several authors.

Supplementary Table 3. Validation of predictive criteria on 10 additional studies not included in the training dataset

Study name	Potential conflict of interest	Country	Pro Con HCQ	Direction of effect of studies of the training set with identical criteria*	Validation of predictive criteria?
Aguila-Gordo, Rev Esp Geriatr Gerontol, 2020	No	Spain	Pro	All 4/4 were Pro	Yes
Aparisi, MedRxiv, 2020	No	Spain	Pro	4/5 were Pro	Yes
Brown, Ann Am Thorac Surg, 2020	Yes	USA	Con	2/2 were Con	Yes
Guisado-Vasco, EClinicalMedicine, 2020	No	Spain	Pro	12/12 were Pro	Yes
Lano, Clin Kidney J, 2020	No	France	Pro	1/1 was Pro	Yes
Namendys-Silva, Heart Lung, 2020	No	Mexico	Pro	4/4 were Pro	Yes
Sands, Int J Infect Dis, 2020	Yes	USA	Con	1/1** was Con	Yes
Solh, MedRxiv, 2020	Yes	USA	Con	1/1 was Con***	Yes
Su, BioSci Trends, 2020	No	China	Pro	9/9 were Pro	Yes
Szente Fonseca, Travel Med Infect Dis, 2020	No	Brazil	Pro	3/3 were Pro	Yes

*Among most significant criteria: Potential conflict of interest, declared funding, known centers, detailed therapeutic protocol, toxic treatment, severity ruled out, Big Data study, observational studies.
**No study with identical criteria was found. One study with only 1 different criterium ("role of severity NOT ruled out" in Singh, MedRxiv, 2020) was selected as a comparator.
***This study suggested a beneficial role of remdesivir.

Study name	Statistics with study removed				Odds ratio (95% CI) with study removed
	Point	Lower limit	Upper limit	p-Value	0.10 0.20 0.50 1.00 2.00 5.00 10.00
Alberici, Kidney International, 2020 - HCQ	0.61	0.52	0.70	0.000000	
Arshad, Int J Infect Dis, 2020 - HCQ +/- AZ	0.60	0.52	0.70	0.000000	
Ayerbe, Intern Emerg Med, 2020 - HCQ	0.61	0.52	0.71	0.000000	
Catteau, Int J Antimicrob Agents, 2020 - HCQ +/- AZ	0.57	0.48	0.69	0.000000	
Derwand, IJAA, 2020 - HCQ+AZ+Zinc	0.61	0.53	0.70	0.000000	
Di Castelnuovo, Eur J Intern Med, 2020 - HCQ	0.58	0.49	0.68	0.000000	
Guerin, Asian J Med Health, 2020 - HCQ+AZ	0.60	0.52	0.70	0.000000	
Lagier, Trav Med Infect Dis, 2020 - HCQ+AZ	0.60	0.52	0.70	0.000000	
Lauriola, Clin Translat Sci, 2020 - HCQ alone	0.60	0.52	0.69	0.000000	
Lauriola, Clin Translat Sci, 2020 - HCQ+AZ	0.65	0.58	0.74	0.000000	
Lecronier, Critical Care, 2020 - HCQ	0.61	0.53	0.70	0.000000	
Membrillo de Novales, Preprints, 2020 - HCQ	0.62	0.53	0.71	0.000000	
Mikami, J Gen Intern Med, 2020 - HCQ	0.59	0.50	0.69	0.000000	
Nachega, Am J Trop Med Hyg, 2020 - HCQ+AZ	0.64	0.56	0.73	0.000000	
Paccoud, Clin Infect Dis, 2020 - HCQ	0.60	0.52	0.70	0.000000	
Sulaiman, MedRxiv, 2020 - HCQ	0.57	0.49	0.67	0.000000	
Yu, Sci China Life Sci, 2020 - HCQ	0.61	0.53	0.71	0.000000	
	0.60	0.52	0.70	0.000000	

This analysis allows to exclude a summary significant effect linked to an aberrant study

Supplementary Fig 1: One-study-removed meta-analysis of observational studies without potential conflict of interest and with detailed therapeutic protocol