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Clinical efficacy of chloroquine derivatives in COVID-19 infection: comparative meta-analysis between the big data and the real world

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6 **Abstract**

7 In the context of the current COVID-19 pandemic, we conducted a meta-analysis on the
8 effects of chloroquine derivatives in patients, based on unpublished and published reports
9 available publicly on the internet as of May, 27, 2020. The keywords “hydroxychloroquine”,
10 “chloroquine”, “coronavirus”, “COVID-19” and “SARS-Cov-2” were used in the PubMed,
11 Google Scholar and Google search engines without any restrictions as to date or language.
12 Twenty studies were identified involving 105,040 patients (19,270 treated patients) from nine
13 countries (Brazil, China, France, Iran, Saudi Arabia, South Korea, Spain, and USA). Big data
14 observational studies were associated with conflict of interest, lack of treatment dosage and
15 duration, and absence of favorable outcome. Clinical studies were associated with favorable
16 outcomes and details on therapy. Among clinical studies, three of four randomized controlled
17 trials reported a significant favorable effect. Among clinical studies, a significant favorable
18 summary effect was observed for duration of cough (Odds ratio (OR), 0.19, $p = .00003$),
19 duration of fever (0.11, $p = .039$), clinical cure (0.21, $p = .0495$), death (0.32, $p = 4.1 \times 10^{-6}$)
20 and viral shedding (0.43, $p = .031$). A trend for a favorable effect was noted for the outcome
21 “death and/or ICU transfer” (0.29, $p = .069$) with a point estimate remarkably similar to that
22 observed for death (~ 0.3). In conclusion, a meta-analysis of publicly available clinical reports
23 demonstrates that chloroquine derivatives are effective to improve clinical and virological
24 outcomes but, more importantly, it reduces mortality by a factor 3 in patients infected with
25 COVID-19. Big data are lacking basic treatment definitions and are linked to conflict of
26 interest.

27 **Introduction**

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

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

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

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

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

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

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

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

83

84 **Methods**

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

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

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

104 Studies were classified as “big data” studies when conducted on electronic medical
105 records extracted by public health specialists and epidemiologists who did not care COVID-
106 19 patients themselves. Conversely, studies were classified as “clinical studies” when
107 mentioning details of treatments (dosages, duration, contraindications, monitoring...) and
108 conducted by authors physicians (infectious diseases and internal medicine specialists, and
109 pulmonologists) who cared COVID-19 patients themselves. Conflicts of interest were
110 retrieved from author statements in the article. Another check was performed using Euros for
111 Docs (<https://www.eurosfordocs.fr/>) and Dollars for Docs
112 (<https://projects.propublica.org/docdollars/>) websites. We considered that there was a conflict
113 of interest when funding by the pharmaceutical industry exceeds 50,000€, over seven years.

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

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

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

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

127

128

129 **Results**

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

140 We noted that registry studies based on electronic medical records did not mentioned
141 the dosage or included several dosages of the chloroquine derivatives used (16-20). We found
142 that in several studies, patients used several molecules with established or potential antiviral
143 properties. For instance, in China and Iran, almost all patients used multiple antivirals:
144 lopinavir/ritonavir, oseltamivir, entecavir, ribavirin, umifenovir and nebulisation of interferon
145 aerosol. In eight studies (15,18-24) patients used the combined therapy that we have
146 recommended (HCQ and AZ combination (9)). Four RCTs were included in this analysis
147 (14,25-27).

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

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

160

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

162 As we observed that several studies reported a clear favorable effect (15, 21-23, 25, 26, 30,
163 32-35) but others reported no (14,16,17,19,24,29) or a clear deleterious effect (18), we
164 primarily performed a unsupervised clustering analysis including the following variables :
165 “Pro” / “Cons” studies, “big data” versus “clinical studies”, “detailed” or “absence of detailed
166 treatment”, presence or absence of a conflict of interest (Figure 1).

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

171 All “big data” studies reported a lack of beneficial effect of the treatment and were
172 significantly more likely associated with “Cons” variable (5/5 vs 3/15, $p = .004$). This was
173 also observed by examination of the meta-analysis forest plot (Figure 2, Table S3 to S8). In
174 addition, both “conflicts of interest” ($p = .01$) and “not described treatment protocol”
175 variables ($p = .004$) were associated with “Cons” variable. Conversely, clinical studies were
176 more likely to report a favorable effect of chloroquine derivatives in COVID-19 patients ($p <$
177 $.05$). Consistently, clinical studies with detailed treatment protocol were more likely
178 associated with the observation of a favorable effect of the treatment ($p < .05$).

179

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

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

184

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

186 We primarily tested if the studies involving direct care of patients (clinical studies performed
187 by physician who took care of patients) were associated with a different direction of effect
188 compared to "big data" studies (Figure 2). The visual examination of the forest plot clearly
189 evidenced that "big data" studies reported no (16,17,19,20) or deleterious effect (18). In
190 contrast, several clinical studies reported significant favorable effects notably regarding
191 hospitalization rate (21), duration of fever (25,33), duration of cough (23,25), clinical cure
192 (15,30), C-reactive protein levels (30), interleukin-6 levels (35), thoracic CT-imaging (25),
193 length of hospital stay (23,26), death or ICU transfer (22,32), death (34,35) and persistent
194 viral shedding (9,23,33).

195 We compared the proportion of comparisons reporting significant differences
196 according to treatment. In the big data analyses, 4 comparisons reported a significant effect,
197 and all were deleterious (4/4). In the clinical studies, 17 comparisons reported a significant
198 effect, and all were beneficial. The difference was highly significant (4/4 vs 0/17, Bilateral
199 Mid-P exact test, $p = .00016$). This was also supported by the significant heterogeneity
200 between the two subgroups (big data vs. clinical studies, mixed effect analysis, Q-value 51.8,
201 $p < .001$).

202

203

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

219

220 **Effect of chloroquine derivatives without azithromycin**

221 As several studies addressed the effectiveness of the combination of chloroquine derivatives
222 with a macrolide, specifically AZ, we tested if the favorable clinical effect (observed in
223 clinical studies) remained after exclusion of comparisons with combination therapy
224 (Supplementary Figure 1). A favorable effect was still observed for duration of cough (n = 1,
225 point estimate 0.12, p = .001), duration of fever (n = 2, 0.05, p = .002), clinical cure (n = 2,
226 0.48, p = .022), C-reactive protein levels (n = 1, 0.55, p = .045), interleukin-6 levels (n = 1,
227 0.43, p = .002), and death (n = 3, 0.31, p < .001). Interestingly, the effect was not significant
228 anymore for persistent viral shedding (n = 7, 0.51, 0.20-1.33, p = 0.17).

229

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

231 We found a favorable summary effect on duration of cough (n = 2, point estimate 0.19, 95%
232 confidence interval 0.09-0.42, p = .00003 – I² = 0%), duration of fever (n = 3, 0.11, 0.01-0.90,
233 p=.039 – I² = 91%, p < .001), clinical cure (n = 3, 0.21, 0.05-1.0, p = .0495 – I² = 81%, p <
234 .001), and death (n = 4, 0.32, 0.19-0.52, p = 4.1 x 10⁻⁶ – I² = 0%, p = .71 – Table S9). A trend
235 for the outcome “death or ICU transfer” was also noted (n = 3, 0.29, 0.08-1.10, p = .069 – I² =
236 85%, p < .002) with a point estimate very similar to that observed for the death outcome (0.3,
237 e.g. a 3 fold decrease in the risk of ICU transfer and/or death). For persistent viral shedding,
238 10 comparisons were included with a significant favorable effect on persistent viral shedding
239 (n = 10, point estimate 0.43, 0.20-0.92, p = .031 – I² = 75%, p < .001).

240

241 **Discussion**

242 Chloroquine derivatives present a paradox. On one hand, the heterogeneity of patients and
243 treatment schemes make it difficult to obtain a clear picture while the epidemic is still
244 ongoing. On the other hand, despite controversy, only chloroquine derivatives have been used
245 by physicians on a large-scale basis as treatment for COVID-19 (36). According to the Sermo
246 Real Time Covid-19 Barometer (<https://www.sermo.com/>, consulted 27 May), for over
247 20,000 physicians across 30 countries, chloroquine derivatives are the first medication used to
248 treat COVID-19 patients in ICUs (43% - except oxygen, anti-clotting / anticoagulants,
249 steroids and norepinephrine) and in other hospital settings (52% - except oxygen), and the
250 second in outpatient settings (33%, after AZ and similar antibiotics).

251 Indeed, we were challenged by the major discrepancies between the results of the
252 various published studies and our experience at the IHU where 7800 ECGs were performed in
253 4000 patients. In order to understand which elements could lead to contradictory results, we

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

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

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

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

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

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

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491

492 **Declaration of competing interest**

493 The authors declare no competing interests. Funding sources had no role in the design and
494 conduct of the study; collection, management, analysis, and interpretation of the data; and
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497

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501 **Figure legends**

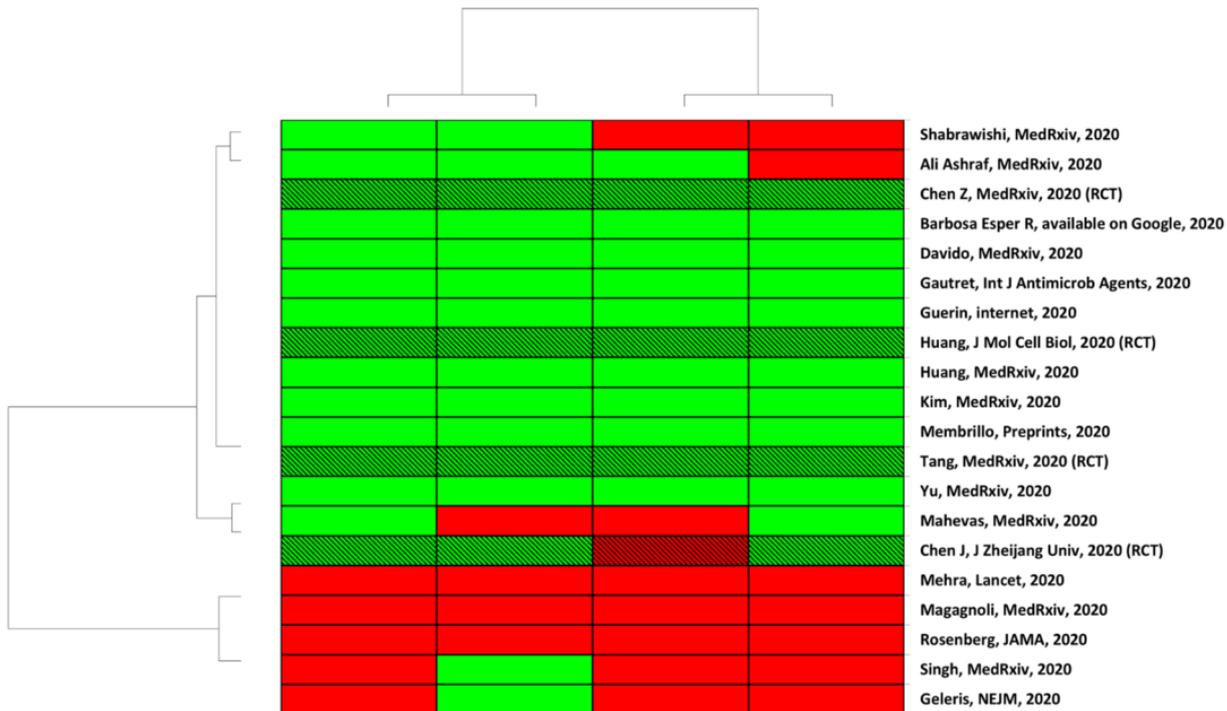
502 **Figure 1. Unsupervised analysis evidencing an association between big data studies, inaccurate**
503 **treatment protocol, conflict of interest and absence of beneficial effect of chloroquine derivative**

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

509

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

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



Clinical Big data No conflict of interest / Conflict of interest Pro / Cons Detailed treatment / Absence of detailed treatment

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

