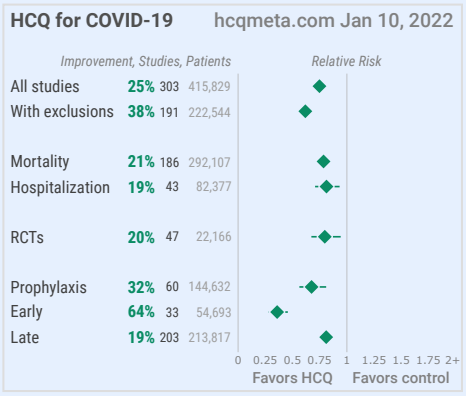
HCQ for COVID-19: real-time meta analysis of 303 studies

Covid Analysis, **Jan 10, 2022**, Version 169 — added McKinnon

https://hcqmeta.com/

- 32 of the 33 early treatment studies report a positive effect. 19 show statistically significant improvements in isolation (14 for the most serious outcome).
- 46 of the 60 pre-exposure prophylaxis studies report a positive effect. 18 show statistically significant improvements in isolation (16 for the most serious outcome). 12 of the 14 negative effects are from studies where all or most patients were autoimmune disorder patients.

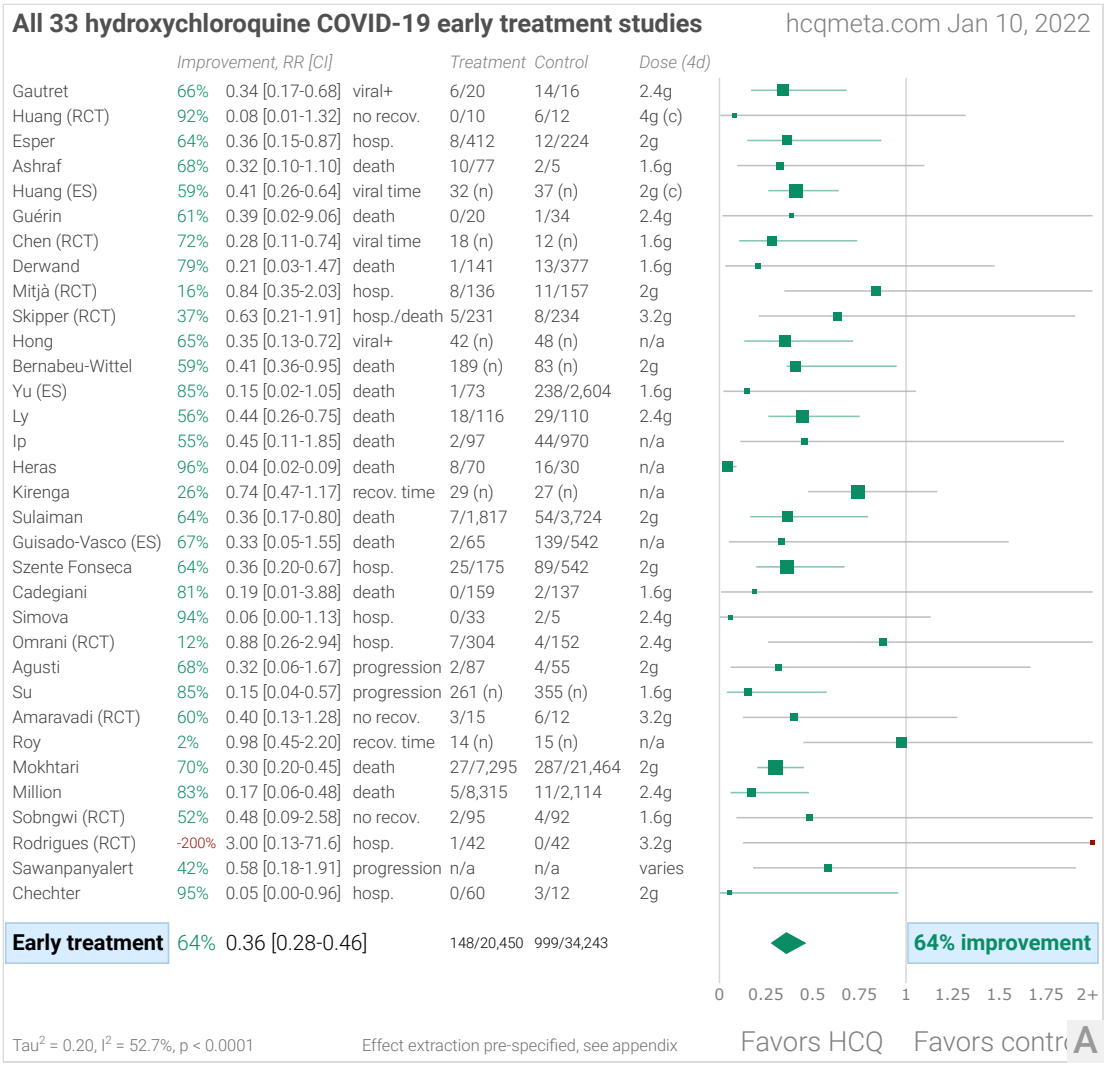


- Late treatment is less successful, with only 67% of the 203 studies reporting a positive effect. Very late stage treatment is not effective and may be harmful, especially when using excessive dosages.
- 84% of Randomized Controlled Trials (RCTs) for early, PrEP, or PEP treatment report positive effects, the probability of results as good or better for an ineffective treatment is 0.0022.
- Meta analysis using the most serious outcome reported shows 64% [54-72%] improvement for the 33 early treatment studies. Results are similar after exclusion based sensitivity analysis and after restriction to peer-reviewed studies. Restricting to the 8 RCTs shows 46% [16-65%] improvement, and restricting to the 13 mortality results shows 75% [60-84%] lower mortality.
- There is evidence of bias towards publishing negative results. 77% of prospective studies report positive effects, compared to 71% of retrospective studies. Studies from North America are 2.7 times more likely to report negative results than studies from the rest of the world combined, p = 0.0000000264. The probability that an ineffective treatment generated results as positive as the 303 studies is estimated to be 1 in 1 quadrillion.
- Negative meta analyses of HCQ generally choose a subset of trials, focusing on late treatment, especially trials with very late treatment and excessive dosages.
- While many treatments have some level of efficacy, they do not replace vaccines and other measures to avoid infection. Only 5% of HCQ studies show zero events in the treatment arm.
- Elimination of COVID-19 is a race against viral evolution. No treatment, vaccine, or intervention is 100% available and effective for all current and future variants. All practical, effective, and safe means should be used. Not doing so increases the risk of COVID-19 becoming endemic; and increases mortality, morbidity, and collateral damage.
- All data to reproduce this paper and the sources are in the appendix. See ***[Ladapo, Prodromos, Risch, Risch (B)]*** for other meta analyses showing efficacy when HCQ is used early.

Total	303 studies	4,814 authors	415,929 patients

Positive effects	220 studies	3,411 authors	293,403 patients

Early treatment	64% improvement	RR 0.36 [0.28-0.46]
Late treatment	19% improvement	RR 0.81 [0.76-0.86]



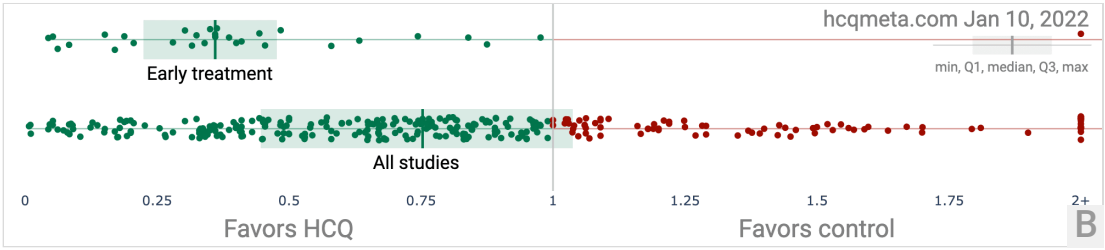


Figure 1. *A. Random effects meta-analysis of all early treatment studies. This plot shows pooled effects, analysis for individual outcomes is below, and more details on pooled effects can be found in the heterogeneity section. Effect extraction is pre-specified, using the most serious outcome reported. Simplified dosages are shown for comparison, these are the total dose in the first four days. Chloroquine is indicated with (c). For details of effect extraction and full dosage information see the appendix.* ***B.*** *Scatter plot of the effects reported in early treatment studies and in all studies. Early treatment is more effective.* ***C and D.*** *Chronological history of all reported effects, with the probability that the observed or greater frequency of positive results were generated by an ineffective treatment.*

Introduction

We analyze all significant studies concerning the use of HCQ (or CQ) for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random-effects meta-analysis results for all studies, for studies within each treatment stage, for mortality results only, after exclusion of studies with critical bias, and for Randomized Controlled Trials (RCTs) only. Typical meta analyses involve subjective selection criteria and bias evaluation, requiring an understanding of the criteria and the accuracy of the evaluations. However, the volume of studies presents an opportunity for an additional simple and transparent analysis aimed at detecting efficacy.

If treatment was not effective, the observed effects would be randomly distributed (or more likely to be negative if treatment is harmful). We can compute the probability that the observed percentage of positive results (or higher) could occur due to chance with an ineffective treatment (the

probability of >= *k* heads in *n* coin tosses, or the one-sided sign test / binomial test). Analysis of publication bias is important and adjustments may be needed if there is a bias toward publishing positive results. For HCQ, we find evidence of a bias toward publishing negative results.

Figure 2 shows stages of possible treatment for COVID-19. Pre-Exposure Prophylaxis (PrEP) refers to regularly taking medication before being infected, in order to prevent or minimize infection. In Post-Exposure Prophylaxis (PEP), medication is taken after exposure but before symptoms appear. Early Treatment refers to treatment immediately or soon after symptoms appear, while Late Treatment refers to more delayed treatment.

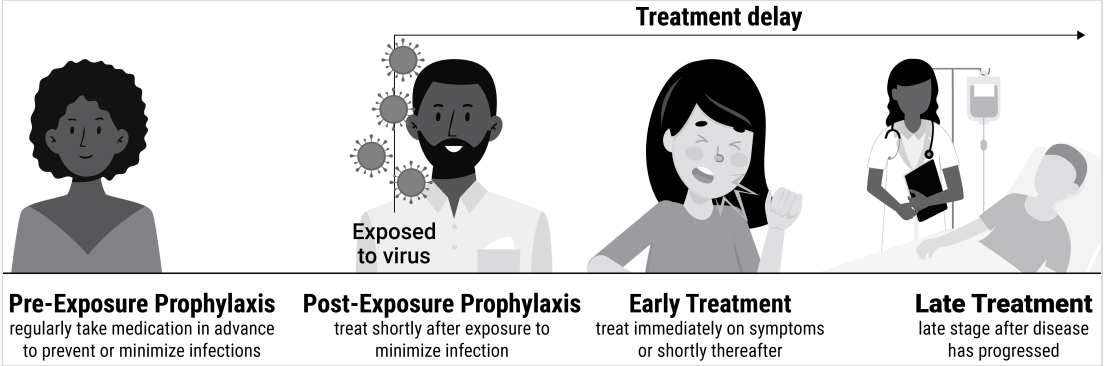


Figure 2. *Treatment stages.*

Results

Figure 3, Figure 4, and Table 1 show results by treatment stage, and Figure 5 shows a forest plot for a random effects meta-analysis of all studies. Figure 6 and Figure 7 show forest plots restricted to mortality and hospitalization results only.

Early treatment. 97% of early treatment studies report a positive effect, with an estimated reduction of 64% in the effect measured (death, hospitalization, etc.) from the random effects meta-analysis, RR 0.36 [0.28-0.46].

Late treatment. Late treatment studies are mixed, with 67% showing positive effects, and an estimated reduction of 19% in the random effects meta-analysis. Negative studies mostly fall into the following categories: they show evidence of significant unadjusted confounding, including confounding by indication; usage is extremely late; or they use an excessively high dosage.

Pre-Exposure Prophylaxis. 77% of PrEP studies show positive effects, with an estimated reduction of 32% in the random effects meta-analysis. Negative studies are all studies of systemic autoimmune disease patients which either do not adjust for the different baseline risk of these patients at all, or do not adjust for the highly variable risk within these patients.

Post-Exposure Prophylaxis. 88% of PEP studies report positive effects, with an estimated reduction of 33% in the random effects meta-analysis.

Treatment time	Number of studies reporting positive results	Total number of studies	Percentage of studies reporting positive results	Probability of an equal or greater percentage of positive results from an ineffective treatment	Random effects meta-analysis results
Early treatment	32	33	**97.0%**	1 in 253 million	**64%** improvement RR 0.36 [0.28-0.46] p < 0.0001
Late treatment	137	204	67.2%	1 in 2 million	19% improvement RR 0.81 [0.76-0.86] p < 0.0001
Pre-Exposure Prophylaxis	47	61	77.0%	1 in 74 thousand	32% improvement RR 0.68 [0.56-0.81] p < 0.0001
Post-Exposure Prophylaxis	7	8	87.5%	1 in 28	33% improvement RR 0.67 [0.53-0.83] p = 0.00043
All studies	220	303	72.6%	1 in 1 quadrillion	25% improvement RR 0.75 [0.71-0.79] p < 0.0001

Table 1. *Results by treatment stage. 3 studies report results for a subset with early treatment, these are not included in the overall results.*

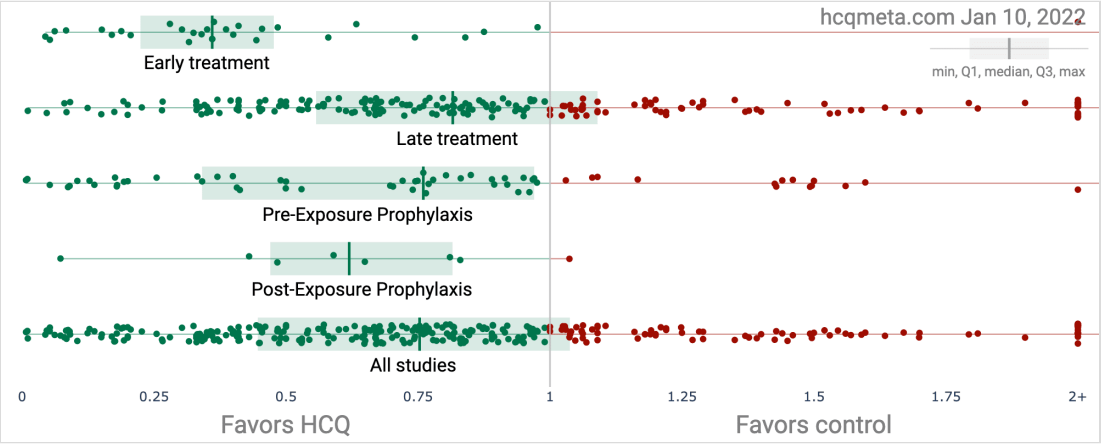


Figure 3. *Results by treatment stage.*

Figure 4. *Chronological history of results by treatment stage, with the probability that the observed or greater frequency of positive results were generated by an ineffective treatment.*

All hydroxychloroquine COVID-19 studies

hcqmeta.com Jan 10, 2022

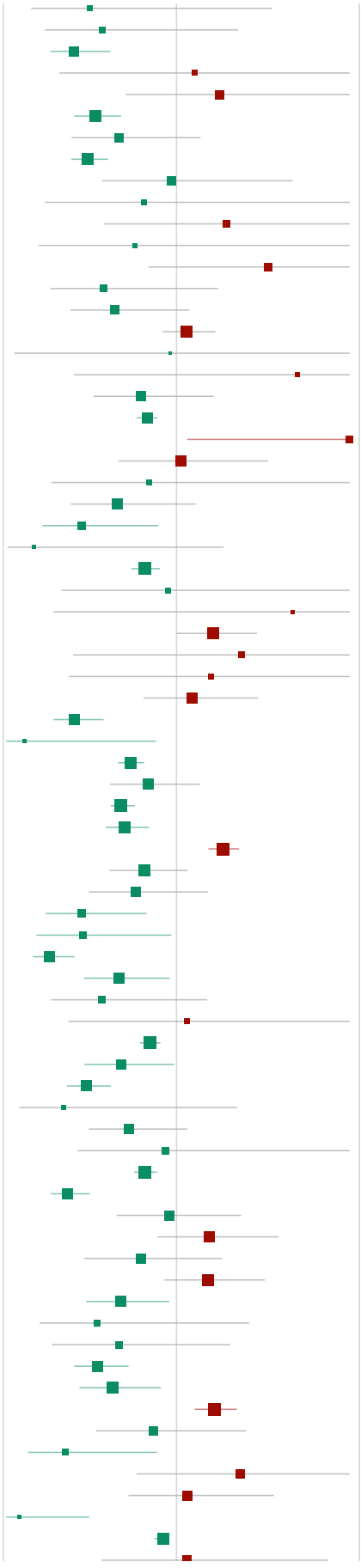
	Improvement	RR [CI]		Treatment	Control
Gautret	66%	0.34 [0.17-0.68]	viral+	6/20	14/16
Huang (RCT)	92%	0.08 [0.01-1.32]	no recov.	0/10	6/12
Esper	64%	0.36 [0.15-0.87]	hosp.	8/412	12/224
Ashraf	68%	0.32 [0.10-1.10]	death	10/77	2/5
Huang (ES)	59%	0.41 [0.26-0.64]	viral time	32 (n)	37 (n)
Guérin	61%	0.39 [0.02-9.06]	death	0/20	1/34
Chen (RCT)	72%	0.28 [0.11-0.74]	viral time	18 (n)	12 (n)
Derwand	79%	0.21 [0.03-1.47]	death	1/141	13/377
Mitjà (RCT)	16%	0.84 [0.35-2.03]	hosp.	8/136	11/157
Skipper (RCT)	37%	0.63 [0.21-1.91]	hosp./death	5/231	8/234
Hong	65%	0.35 [0.13-0.72]	viral+	42 (n)	48 (n)
Bernabeu-Wittel	59%	0.41 [0.36-0.95]	death	189 (n)	83 (n)
Yu (ES)	85%	0.15 [0.02-1.05]	death	1/73	238/2,604
Ly	56%	0.44 [0.26-0.75]	death	18/116	29/110
Ip	55%	0.45 [0.11-1.85]	death	2/97	44/970
Heras	96%	0.04 [0.02-0.09]	death	8/70	16/30
Kirenga	26%	0.74 [0.47-1.17]	recov. time	29 (n)	27 (n)
Sulaiman	64%	0.36 [0.17-0.80]	death	7/1,817	54/3,724
Guisado-Vasco (ES)	67%	0.33 [0.05-1.55]	death	2/65	139/542
Szente Fonseca	64%	0.36 [0.20-0.67]	hosp.	25/175	89/542
Cadegiani	81%	0.19 [0.01-3.88]	death	0/159	2/137
Simova	94%	0.06 [0.00-1.13]	hosp.	0/33	2/5
Omrani (RCT)	12%	0.88 [0.26-2.94]	hosp.	7/304	4/152
Agusti	68%	0.32 [0.06-1.67]	progression	2/87	4/55
Su	85%	0.15 [0.04-0.57]	progression	261 (n)	355 (n)
Amaravadi (RCT)	60%	0.40 [0.13-1.28]	no recov.	3/15	6/12
Roy	2%	0.98 [0.45-2.20]	recov. time	14 (n)	15 (n)
Mokhtari	70%	0.30 [0.20-0.45]	death	27/7,295	287/21,464
Million	83%	0.17 [0.06-0.48]	death	5/8,315	11/2,114
Sobngwi (RCT)	52%	0.48 [0.09-2.58]	no recov.	2/95	4/92
Rodrigues (RCT)	-200%	3.00 [0.13-71.6]	hosp.	1/42	0/42
Sawanpanyalert	42%	0.58 [0.18-1.91]	progression	n/a	n/a
Chechter	95%	0.05 [0.00-0.96]	hosp.	0/60	3/12
Early treatment	64%	0.36 [0.28-0.46]		148/20,450	999/34,243

64% improvement

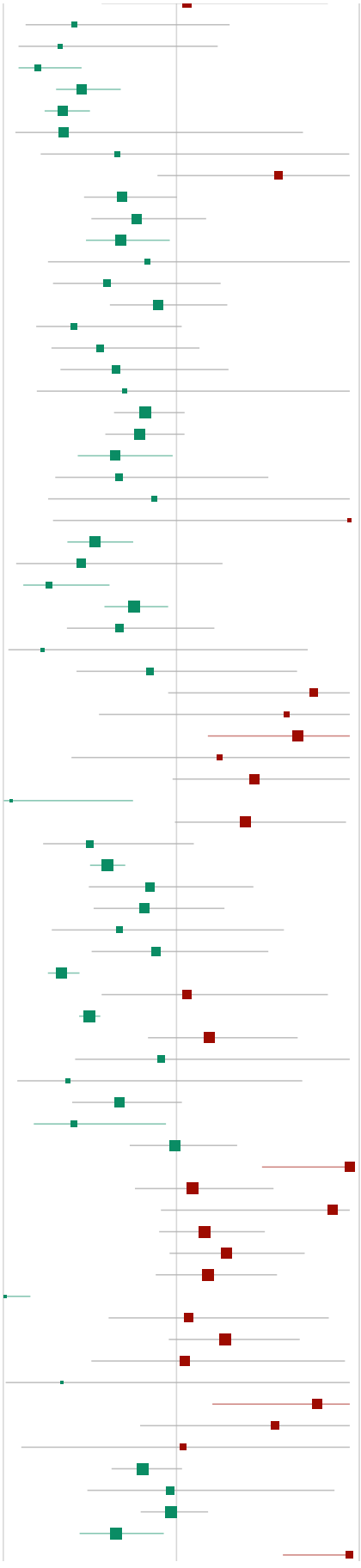
$Tau^2 = 0.20$, $I^2 = 52.7\%$, $p < 0.0001$

	Improvement	RR [CI]		Treatment	Control
Xia	38%	0.62 [0.32-1.22]	viral+	5/10	12/15
Chen (RCT)	29%	0.71 [0.29-1.74]	progression	5/15	7/15
Zhong	80%	0.20 [0.08-0.52]	viral+	5/115	17/82
Chen (RCT)	57%	0.43 [0.19-0.97]	pneumonia	6/31	14/31
Barbosa	-147%	2.47 [0.24-25.0]	death	2/17	1/21
Tang (RCT)	21%	0.79 [0.38-1.62]	viral+	11/75	14/75
Magagnoli	11%	0.89 [0.45-1.77]	death	39/148	18/163
Auld	-3%	1.03 [0.67-1.57]	death	33/114	29/103
Sánchez-Álvarez	46%	0.54 [0.34-0.84]	death	322 (n)	53 (n)
Mallat	-203%	3.03 [1.11-7.69]	viral time	23 (n)	11 (n)
Membrillo de Nov..	55%	0.45 [0.29-0.71]	death	27/123	21/43
Geleris	-4%	1.04 [0.82-1.32]	int./death	262/811	84/565
Alberici	43%	0.57 [0.24-1.13]	death	17/72	9/22
Rosenberg	-35%	1.35 [0.76-2.40]	death	189/735	28/221
Shabrawishi	15%	0.85 [0.45-1.62]	viral+	12/45	15/48
Mahévas	-20%	1.20 [0.40-3.30]	death	9/84	8/89
Yu	60%	0.40 [0.22-0.72]	death	9/48	238/502
Kim	51%	0.49 [0.28-0.87]	hosp. time	22/22	40/40
Singh	5%	0.95 [0.74-1.22]	death	104/910	109/910
Luo	32%	0.68 [0.08-5.88]	death	19 (n)	264 (n)
Hraiech	65%	0.35 [0.08-1.56]	death	2/17	5/15
Ip	1%	0.99 [0.80-1.22]	death	432/1,914	115/598
Goldman	22%	0.78 [0.40-1.52]	death	10/109	34/288
Huang	67%	0.33 [0.19-0.57]	viral time	197 (n)	176 (n)
Kuderer	-134%	2.34 [1.62-3.21]	death	45/181	121/928
Rogado	92%	0.08 [0.00-0.87]	death	1/8	7/9
RECOVERY (RCT)	-9%	1.09 [0.97-1.23]	death	421/1,561	790/3,155
Wang	6%	0.94 [0.75-1.19]	death	1,866 (n)	5,726 (n)
Luo	-2%	1.02 [0.39-2.65]	death	11/35	4/13
Paccoud	11%	0.89 [0.23-3.47]	death	21/38	26/46
Sbidian	-5%	1.05 [0.77-1.33]	death	111/623	830/3,792
Faíco-Filho	81%	0.19 [0.00-8.66]	viral rate	34 (n)	32 (n)

Fontana	50%	0.50 [0.16-1.55]	death	4/12	2/3
Bousquet	43%	0.57 [0.24-1.36]	death	5/27	23/81
Lagier	59%	0.41 [0.27-0.62]	death	35/3,119	58/618
Sosa-García	-11%	1.11 [0.32-3.78]	death	7/38	3/18
Komissarov	-25%	1.25 [0.71-2.21]	viral load	26/26	10/10
Mikami	47%	0.53 [0.41-0.68]	death	575/2,077	231/743
Martinez-Lopez	33%	0.67 [0.39-1.14]	death	47/148	9/19
Arshad	51%	0.49 [0.39-0.60]	death	162/1,202	108/409
An	3%	0.97 [0.57-1.67]	viral+	31/31	195/195
Rivera-Izquierdo	19%	0.81 [0.24-2.76]	death	215 (n)	23 (n)
Chen	-29%	1.29 [0.58-2.86]	viral+	16/28	4/9
Chen (RCT)	24%	0.76 [0.20-2.84]	viral+	4/21	3/12
Cravedi	-53%	1.53 [0.84-2.80]	death	36/101	10/43
Lecronier	42%	0.58 [0.27-1.24]	death	9/38	9/22
Trullàs	36%	0.64 [0.39-1.07]	death	20/66	16/34
Gupta	-6%	1.06 [0.92-1.22]	death	631/1,761	153/454
Lyngbakken (RCT)	4%	0.96 [0.06-14.6]	death	1/27	1/26
McGrail	-70%	1.70 [0.41-7.07]	death	4/33	3/42
Krishnan	20%	0.80 [0.52-1.21]	death	86/144	6/8
Bernaola	17%	0.83 [0.77-0.89]	death	236/1,498	28/147
Kelly	-143%	2.43 [1.06-5.56]	death	23/82	6/52
Rivera	-2%	1.02 [0.67-1.53]	death	44/179	59/327
Cavalcanti (RCT)	16%	0.84 [0.28-2.53]	death	8/331	5/173
D'Arminio Monforte	34%	0.66 [0.39-1.11]	death	53/197	47/92
Davido	55%	0.45 [0.23-0.89]	int./hosp.	12/80	13/40
Yu	83%	0.17 [0.02-1.27]	progression	1/231	32/1,291
Berenguer	18%	0.82 [0.74-0.90]	death	681/2,618	438/1,377
Kamran	5%	0.95 [0.34-2.69]	progression	11/349	5/151
Kalligeros	-67%	1.67 [0.29-9.36]	death	36 (n)	72 (n)
Saleemi	-21%	1.21 [1.00-1.46]	viral time	65 (n)	20 (n)
Roomi	-38%	1.38 [0.40-2.76]	death	13/144	6/32
Abd-Elsalam (RCT)	-20%	1.20 [0.38-3.80]	death	6/97	5/97
Peters	-9%	1.09 [0.81-1.47]	death	419/1,596	53/353
Pinato	59%	0.41 [0.29-0.58]	death	30/182	181/446
Dubernet	88%	0.12 [0.02-0.88]	ICU	1/17	9/19
Gonzalez	27%	0.73 [0.66-0.81]	death	1,246/8,476	341/1,168
Pasquini	16%	0.84 [0.62-1.14]	death	23/33	15/18
Catteau	32%	0.68 [0.62-0.76]	death	804/4,542	957/3,533
Di Castelnuovo	30%	0.70 [0.59-0.84]	death	386/2,634	90/817
Fried	-27%	1.27 [1.18-1.36]	death	1,048/4,232	1,466/7,489
Albani	18%	0.82 [0.61-1.06]	death	60/211	172/605
Synolaki	24%	0.76 [0.49-1.18]	death	21/98	60/214
Alamdari	55%	0.45 [0.25-0.83]	death	54/427	9/32
Heberto	54%	0.46 [0.19-0.97]	death	139 (n)	115 (n)
Lauriola	74%	0.27 [0.17-0.41]	death	102/297	35/63
Ashinyo	33%	0.67 [0.47-0.96]	hosp. time	61/61	61/61
Serrano	43%	0.57 [0.28-1.18]	death	6/14	6/8
Ulrich (RCT)	-6%	1.06 [0.38-2.98]	death	7/67	6/61
Shoaibi	15%	0.85 [0.79-0.91]	death	686/5,047	3,923/24,404
Lammers	32%	0.68 [0.47-0.99]	death/ICU	30/189	101/498
Ayerbe	52%	0.48 [0.37-0.62]	death	237/1,857	49/162
Almazrou	65%	0.35 [0.09-1.35]	ventilation	3/95	6/66
Nachega	28%	0.72 [0.49-1.06]	death	69/630	28/96
Ader (RCT)	6%	0.94 [0.43-2.05]	death	11/145	12/148
Soto-Becerra	18%	0.82 [0.76-0.89]	death	346/692	1,606/2,630
Aparisi	63%	0.37 [0.27-0.50]	death	122/605	27/49
Annie	4%	0.96 [0.65-1.37]	death	48/367	50/367
SOLIDARITY (RCT)	-19%	1.19 [0.89-1.59]	death	104/947	84/906
Guisado-Vasco	20%	0.80 [0.47-1.26]	death	127/558	14/49
Solh	-18%	1.18 [0.93-1.51]	death	131/265	134/378
Ñamendys-Silva	32%	0.68 [0.48-0.96]	death	24/54	42/64
Dubee (RCT)	46%	0.54 [0.21-1.42]	death	6/124	11/123
Lano	33%	0.67 [0.28-1.31]	death	56 (n)	66 (n)
Coll	46%	0.54 [0.41-0.72]	death	55/307	108/328
Frontera (PSM)	37%	0.63 [0.44-0.91]	death	121/1,006	424/2,467
Choi	-22%	1.22 [1.10-1.35]	viral time	701/701	701/701
Tehrani	13%	0.87 [0.54-1.40]	death	16/65	54/190
López	64%	0.36 [0.14-0.89]	progression	5/36	14/36
Salazar	-37%	1.37 [0.77-2.42]	death	12/92	80/811
Rodriguez-Nava	-6%	1.06 [0.72-1.56]	death	22/65	79/248
Maldonado	91%	0.09 [0.02-0.50]	death	1/11	1/1
Núñez-Gil	8%	0.92 [0.87-0.94]	death	200/686	100/268
Solf (RCT)	-6%	1.06 [0.57-1.87]	death	25/241	25/236



Seif (RCT)	-6%	1.06 [0.57-1.87]	death	25/241	25/236
Rodriguez	59%	0.41 [0.13-1.31]	death	8/39	2/4
Águila-Gordo	67%	0.33 [0.09-1.24]	death	151/346	47/70
Sheshah	80%	0.20 [0.09-0.45]	death	267 (n)	33 (n)
Boari	55%	0.45 [0.30-0.68]	death	41/202	25/56
Budhiraja	65%	0.35 [0.24-0.50]	death	69/834	34/142
Falcone (PSM)	65%	0.35 [0.07-1.73]	death	40/238	30/77
Qin	34%	0.66 [0.22-2.00]	death	3/43	75/706
Burdick	-59%	1.59 [0.89-2.83]	death	142 (n)	148 (n)
van Halem	32%	0.68 [0.47-1.00]	death	34/164	47/155
Rodriguez-Gonzalez	23%	0.77 [0.51-1.17]	death	251/1,148	17/60
Lambermont	32%	0.68 [0.48-0.96]	death	97/225	14/22
Abdulrahman (PSM)	17%	0.83 [0.26-2.69]	death	5/223	6/223
Capsoni	40%	0.60 [0.29-1.25]	ventilation	12/40	6/12
Peng	11%	0.89 [0.62-1.29]	progression	29/453	256/3,567
Modrák	59%	0.41 [0.19-1.03]	death	108 (n)	105 (n)
Ozturk	44%	0.56 [0.28-1.13]	death	165/1,127	6/23
Guglielmetti	35%	0.65 [0.33-1.30]	death	181 (n)	37 (n)
Johnston (RCT)	30%	0.70 [0.19-2.54]	hosp.	5/148	4/83
Alqassieh	18%	0.82 [0.64-1.05]	hosp. time	63 (n)	68 (n)
Bielza	22%	0.78 [0.59-1.05]	death	33/91	249/539
Tan	35%	0.65 [0.43-0.98]	hosp. time	8 (n)	277 (n)
Naseem	33%	0.67 [0.30-1.53]	death	77 (n)	1,137 (n)
Orioli	13%	0.87 [0.26-2.94]	death	8/55	3/18
De Luna	-105%	2.05 [0.29-14.6]	death	15/132	1/18
Signes-Costa	47%	0.53 [0.37-0.75]	death	4,854 (n)	993 (n)
Matangila	55%	0.45 [0.07-1.27]	death	25/147	8/13
Cangiano	73%	0.27 [0.12-0.61]	death	5/33	37/65
Taccone	25%	0.75 [0.58-0.95]	death	449/1,308	183/439
Chari	33%	0.67 [0.37-1.22]	death	8/29	195/473
Güner	77%	0.23 [0.03-1.76]	ICU	604 (n)	100 (n)
Vernaz (PSM)	15%	0.85 [0.42-1.70]	death	12/93	16/105
Texeira	-79%	1.79 [0.95-3.38]	death	17/65	14/96
Psevdos	-63%	1.63 [0.55-4.84]	death	17/52	3/15
Sands	-70%	1.70 [1.18-2.42]	death	101/973	56/696
Lotfy	-25%	1.25 [0.39-3.96]	death	6/99	5/103
Sarfaraz	-45%	1.45 [0.98-2.15]	death	40/94	27/92
Yegerov	95%	0.05 [0.00-0.75]	death	0/23	20/1,049
Li	-40%	1.40 [0.99-1.98]	viral time	18 (n)	19 (n)
Li	50%	0.50 [0.23-1.10]	no disch.	14 (n)	14 (n)
Di Castelnuovo	40%	0.60 [0.50-0.70]	death	3,270 (n)	1,000 (n)
Roig	16%	0.84 [0.49-1.44]	death	33/67	7/12
Ubaldo	18%	0.82 [0.52-1.28]	death	17/25	5/6
Ouedraogo	33%	0.67 [0.28-1.62]	death	397 (n)	59 (n)
Hernandez-C.. (RCT)	12%	0.88 [0.51-1.53]	death	106 (n)	108 (n)
Purwati (RCT)	66%	0.34 [0.26-0.44]	viral+	38/121	111/119
Thompson (RCT)	-6%	1.06 [0.57-1.87]	death	25/241	25/236
Lora-Tamayo	50%	0.50 [0.44-0.56]	death	7,192 (n)	1,361 (n)
Awad	-19%	1.19 [0.84-1.70]	death	56/188	37/148
Lamback	9%	0.91 [0.41-2.00]	death	11/101	11/92
Gonzalez (RCT)	63%	0.37 [0.08-1.73]	death	2/33	6/37
Salvador	33%	0.67 [0.40-1.03]	death	28/121	58/124
Martin-Vicente	59%	0.41 [0.18-0.94]	death	37/91	1/1
Stewart	1%	0.99 [0.73-1.35]	death	66/578	188/1,243
Stewart	-130%	2.30 [1.49-3.54]	death	32/108	33/256
Stewart	-9%	1.09 [0.76-1.56]	death	212/1,157	203/1,101
Stewart	-90%	1.90 [0.91-4.10]	death	46/208	47/1,334
Stewart	-16%	1.16 [0.90-1.51]	death	428/1,711	123/688
Stewart	-29%	1.29 [0.96-1.74]	ventilation	48/305	95/1,302
Stewart	-18%	1.18 [0.88-1.58]	death	90/429	141/737
Barry	99%	0.01 [0.00-0.16]	death	0/6	91/599
Alghamdi	-7%	1.07 [0.61-1.88]	death	44/568	15/207
Mulhem	-28%	1.28 [0.96-1.71]	death	435/2,496	81/723
Gadhiya	-5%	1.05 [0.51-1.97]	death	22/55	33/216
Reis (RCT)	66%	0.34 [0.01-8.30]	death	0/214	1/227
Mohandas	-81%	1.81 [1.21-2.72]	death	27/384	115/2,961
Réa-Neto (RCT)	-57%	1.57 [0.79-3.13]	death	16/53	10/52
Kokturk	-4%	1.04 [0.10-7.64]	death	62/1,382	5/118
Aghajani	19%	0.81 [0.62-1.03]	death	553 (n)	438 (n)
Bosaeed (RCT)	4%	0.96 [0.49-1.91]	death	14/125	15/129
Çiyiltepe	3%	0.97 [0.79-1.18]	death	69/95	39/52
De Rosa	35%	0.65 [0.44-0.93]	death	118/731	80/280
Sammartino (PSM)	-240%	3.40 [1.61-7.40]	death	137 (n)	191 (n)



Smith	27%	0.73 [0.58-0.87]	death	19/37	182/218
Ramírez-García	67%	0.33 [0.22-0.50]	death	48/350	22/53
Sivapalan (RCT)	92%	0.08 [0.00-11.7]	death	1/61	2/56
Byakika-Kib.. (RCT)	0%	1.00 [0.56-1.75]	recov. time	36 (n)	29 (n)
Lagier	32%	0.68 [0.52-0.88]	death	93/1,270	146/841
Singh (RCT)	48%	0.53 [0.15-1.82]	death	3/20	6/21
Saib (PSM)	-125%	2.25 [0.74-6.85]	int./death	9/52	4/52
Turrini	10%	0.90 [0.75-1.03]	death	103/160	33/45
Schwartz (RCT)	-133%	2.33 [0.10-56.1]	ICU	1/111	0/37
Gerlovin	-22%	1.22 [0.91-1.63]	death	90/429	141/770
Taieb	39%	0.61 [0.41-0.92]	no disch.	674 (n)	252 (n)
Jacobs	7%	0.93 [0.69-1.27]	death	24/46	86/154
Roger	0%	1.00 [0.65-1.45]	death	53/289	120/677
Barrat-Due (RCT)	-120%	2.20 [0.40-10.8]	death	4/45	2/48
Alhamlan	-52%	1.52 [0.24-5.23]	death	n/a	n/a
Barra	11%	0.89 [0.24-3.35]	death	2/18	81/650
Alghamdi	-39%	1.39 [0.66-2.95]	death	29/128	7/43
Alotaibi	-134%	2.33 [0.99-5.49]	death	193 (n)	244 (n)
Çivriz Bozdağ	-399%	4.99 [1.74-14.3]	death	35 (n)	140 (n)
Uygen	12%	0.88 [0.77-1.00]	viral time	15 (n)	25 (n)
Menardi	35%	0.65 [0.39-1.07]	death	32/200	19/77
Babalola (RCT)	-55%	1.55 [0.88-2.72]	no disch.	17/30	11/30
Guglielmetti	28%	0.72 [0.48-1.08]	death	474 (n)	126 (n)
Sarhan (RCT)	26%	0.74 [0.38-1.44]	death	12/56	15/52
Calderón	-215%	3.15 [0.40-24.7]	death	5/27	1/17
Ferreira	-151%	2.51 [1.09-4.43]	death	17/111	11/81
Late treatment	19%	0.81 [0.76-0.86]		16,152/106,085	19,069/107,732

$Tau^2 = 0.11$, $I^2 = 83.7\%$, $p < 0.0001$

	Improvement, RR [CI]			*Treatment*	*Control*
Huh	-43%	1.43 [0.96-2.11]	cases		
Gendelman	8%	0.92 [0.31-2.72]	cases	3/36	1,314/14,484
Konig	3%	0.97 [0.65-1.46]	hosp.	16/29	29/51
Cassione	-50%	1.50 [0.34-6.53]	cases	10/127	2/38
Macias	26%	0.74 [0.07-8.18]	hosp.	1/290	2/432
Gianfrancesco	3%	0.97 [0.71-1.24]	hosp.	58/130	219/470
Chatterjee	67%	0.33 [0.20-0.56]	cases	12/68	206/387
Bhattacharya	81%	0.19 [0.07-0.53]	cases	4/54	20/52
Huang	80%	0.20 [0.08-0.52]	hosp.	8/8	1,247/1,247
Gendebien	4%	0.96 [0.38-2.46]	cases	12/152	6/73
Ferreira	47%	0.53 [0.39-0.72]	cases	population-based cohort	
Zhong	91%	0.09 [0.01-0.94]	cases	7/16	20/27
Desbois	17%	0.83 [0.27-2.58]	cases	3/27	23/172
Kadnur	86%	0.14 [0.02-0.86]	cases	2/248	5/86
Khurana	51%	0.49 [0.24-0.98]	cases	6/22	88/159
Singer	-9%	1.09 [0.79-1.51]	cases	55/10,700	104/22,058
Salvarani	6%	0.94 [0.66-1.34]	cases	population-based cohort	
Ferri	63%	0.37 [0.16-0.83]	cases	9/994	16/647
de la Iglesia	-50%	1.50 [0.25-8.95]	hosp.	3/687	2/688
Laplana	-56%	1.56 [0.74-3.28]	cases	17/319	11/319
Rentsch	-3%	1.03 [0.80-1.33]	death	population-based cohort	
Grau-Pujol (RCT)	11%	0.89 [0.06-14.2]	cases	1/142	1/127
Rajasingham (RCT)	50%	0.50 [0.03-7.97]	hosp.	1/989	1/494
Gentry	91%	0.09 [0.00-1.52]	death	0/10,703	7/21,406
Abella (RCT)	5%	0.95 [0.25-3.63]	cases	4/64	4/61
Yadav	82%	0.18 [0.04-0.81]	hosp.	2/279	9/221
Goenka	87%	0.13 [0.02-0.85]	IgG+	1/77	115/885
Arleo	50%	0.50 [0.06-4.02]	death	1/20	5/50
Behera	28%	0.72 [0.32-1.24]	cases	7/19	179/353
Datta	22%	0.78 [0.42-1.45]	cases	16/146	19/135
Mathai	90%	0.10 [0.05-0.21]	cases	10/491	22/113
Revollo (PSM)	23%	0.77 [0.35-1.68]	cases	16/69	65/418
Jung	59%	0.41 [0.02-9.97]	death	0/649	1/1,417
Gönenli	30%	0.70 [0.20-2.46]	progression	3/148	12/416
Huh	-251%	3.51 [0.76-16.2]	progression	5/8	873/2,797
Cordtz	24%	0.76 [0.23-2.52]	hosp.	population-based cohort	
Rangel	25%	0.75 [0.25-2.24]	death	4/50	11/103
Trefond	-17%	1.17 [0.33-3.54]	death	4/68	12/183
Fitzgerald	9%	0.91 [0.69-1.21]	cases	65/1,072	200/3,594
Bae (PSM)	30%	0.70 [0.41-1.18]	cases	16/743	91/2,698
Pham	20%	0.80 [0.15-2.79]	death	2/14	5/28
Vivanco-Hidalgo	-46%	1.46 [0.91-2.34]	hosp.	40/6,746	50/13,492

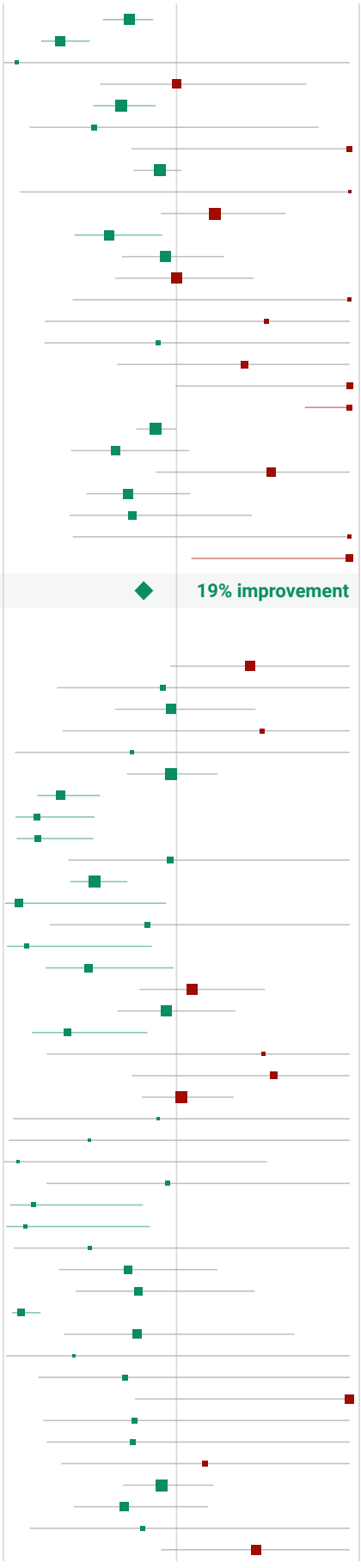


Figure 5. *Random effects meta-analysis. This plot shows pooled effects, analysis for individual outcomes is below, and more details on pooled effects can be found in the heterogeneity section. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. (ES) indicates the early treatment subset of a study (these are not included in the overall results).*

All 188 hydroxychloroquine COVID-19 mortality results

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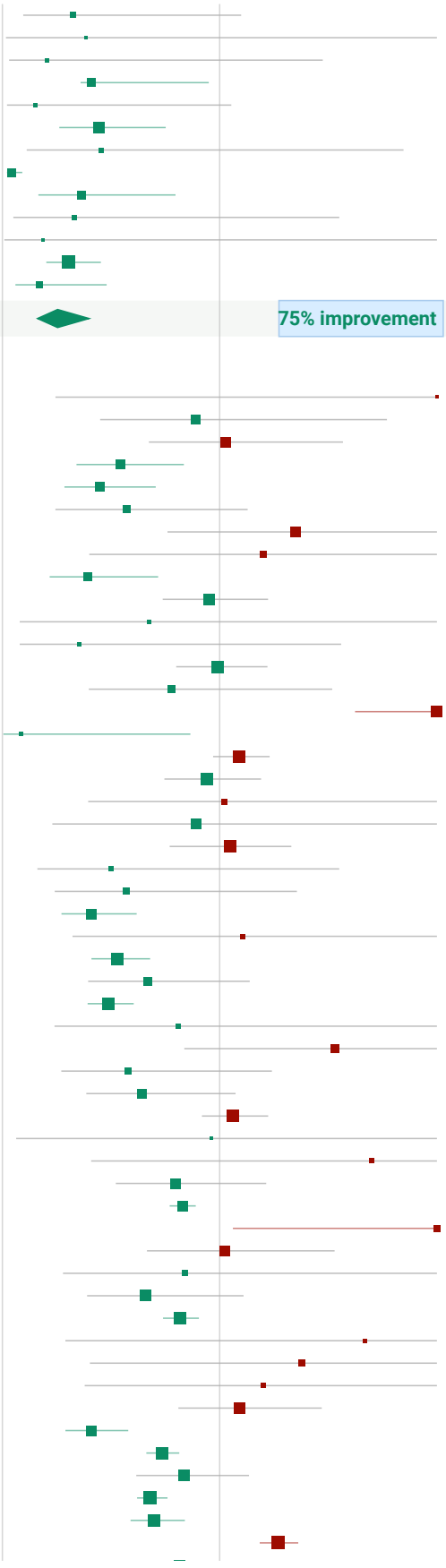
	Improvement	RR [CI]	Treatment	Control
Ashraf	68%	0.32 [0.10-1.10]	10/77	2/5
Guérin	61%	0.39 [0.02-9.06]	0/20	1/34
Derwand	79%	0.21 [0.03-1.47]	1/141	13/377
Bernabeu-Wittel	59%	0.41 [0.36-0.95]	189 (n)	83 (n)
Yu (ES)	85%	0.15 [0.02-1.05]	1/73	238/2,604
Ly	56%	0.44 [0.26-0.75]	18/116	29/110
Ip	55%	0.45 [0.11-1.85]	2/97	44/970
Heras	96%	0.04 [0.02-0.09]	8/70	16/30
Sulaiman	64%	0.36 [0.17-0.80]	7/1,817	54/3,724
Guisado-Vasco (ES)	67%	0.33 [0.05-1.55]	2/65	139/542
Cadegiani	81%	0.19 [0.01-3.88]	0/159	2/137
Mokhtari	70%	0.30 [0.20-0.45]	27/7,295	287/21,464
Million	83%	0.17 [0.06-0.48]	5/8,315	11/2,114
Early treatment	75%	0.25 [0.16-0.40]	81/18,434	836/32,194

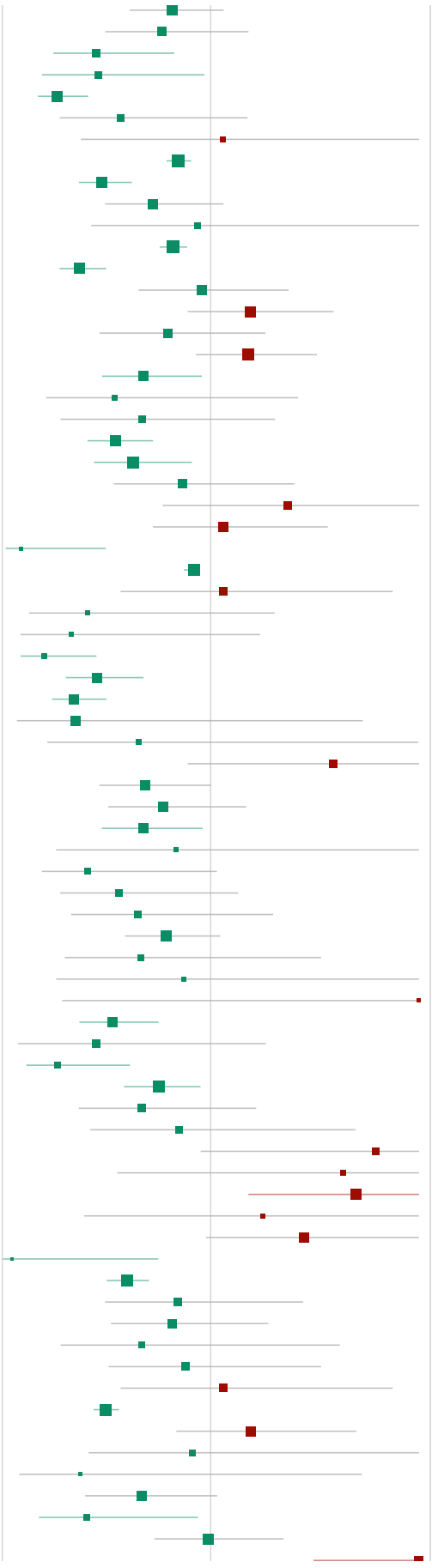
75% improvement

$Tau^2 = 0.33$, $I^2 = 61.1\%$, $p < 0.0001$

	Improvement	RR [CI]	Treatment	Control
Barbosa	-147%	2.47 [0.24-25.0]	2/17	1/21
Magagnoli	11%	0.89 [0.45-1.77]	39/148	18/163
Auld	-3%	1.03 [0.67-1.57]	33/114	29/103
Sánchez-Álvarez	46%	0.54 [0.34-0.84]	322 (n)	53 (n)
Membrillo de Nov..	55%	0.45 [0.29-0.71]	27/123	21/43
Alberici	43%	0.57 [0.24-1.13]	17/72	9/22
Rosenberg	-35%	1.35 [0.76-2.40]	189/735	28/221
Mahévas	-20%	1.20 [0.40-3.30]	9/84	8/89
Yu	60%	0.40 [0.22-0.72]	9/48	238/502
Singh	5%	0.95 [0.74-1.22]	104/910	109/910
Luo	32%	0.68 [0.08-5.88]	19 (n)	264 (n)
Hraiech	65%	0.35 [0.08-1.56]	2/17	5/15
Ip	1%	0.99 [0.80-1.22]	432/1,914	115/598
Goldman	22%	0.78 [0.40-1.52]	10/109	34/288
Kuderer	-134%	2.34 [1.62-3.21]	45/181	121/928
Rogado	92%	0.08 [0.00-0.87]	1/8	7/9
RECOVERY (RCT)	-9%	1.09 [0.97-1.23]	421/1,561	790/3,155
Wang	6%	0.94 [0.75-1.19]	1,866 (n)	5,726 (n)
Luo	-2%	1.02 [0.39-2.65]	11/35	4/13
Paccoud	11%	0.89 [0.23-3.47]	21/38	26/46
Sbidian	-5%	1.05 [0.77-1.33]	111/623	830/3,792
Fontana	50%	0.50 [0.16-1.55]	4/12	2/3
Bousquet	43%	0.57 [0.24-1.36]	5/27	23/81
Lagier	59%	0.41 [0.27-0.62]	35/3,119	58/618
Sosa-García	-11%	1.11 [0.32-3.78]	7/38	3/18
Mikami	47%	0.53 [0.41-0.68]	575/2,077	231/743
Martinez-Lopez	33%	0.67 [0.39-1.14]	47/148	9/19
Arshad	51%	0.49 [0.39-0.60]	162/1,202	108/409
Rivera-Izquierdo	19%	0.81 [0.24-2.76]	215 (n)	23 (n)
Cravedi	-53%	1.53 [0.84-2.80]	36/101	10/43
Lecronier	42%	0.58 [0.27-1.24]	9/38	9/22
Trullàs	36%	0.64 [0.39-1.07]	20/66	16/34
Gupta	-6%	1.06 [0.92-1.22]	631/1,761	153/454
Lyngbakken (RCT)	4%	0.96 [0.06-14.6]	1/27	1/26
McGrail	-70%	1.70 [0.41-7.07]	4/33	3/42
Krishnan	20%	0.80 [0.52-1.21]	86/144	6/8
Bernaola	17%	0.83 [0.77-0.89]	236/1,498	28/147
Kelly	-143%	2.43 [1.06-5.56]	23/82	6/52
Rivera	-2%	1.02 [0.67-1.53]	44/179	59/327
Cavalcanti (RCT)	16%	0.84 [0.28-2.53]	8/331	5/173
D'Arminio Monforte	34%	0.66 [0.39-1.11]	53/197	47/92
Berenguer	18%	0.82 [0.74-0.90]	681/2,618	438/1,377
Kalligeros	-67%	1.67 [0.29-9.36]	36 (n)	72 (n)
Roomi	-38%	1.38 [0.40-2.76]	13/144	6/32
Abd-Elsalam (RCT)	-20%	1.20 [0.38-3.80]	6/97	5/97
Peters	-9%	1.09 [0.81-1.47]	419/1,596	53/353
Pinato	59%	0.41 [0.29-0.58]	30/182	181/446
Gonzalez	27%	0.73 [0.66-0.81]	1,246/8,476	341/1,168
Pasquini	16%	0.84 [0.62-1.14]	23/33	15/18
Catteau	32%	0.68 [0.62-0.76]	804/4,542	957/3,533
Di Castelnuovo	30%	0.70 [0.59-0.84]	386/2,634	90/817
Fried	-27%	1.27 [1.18-1.36]	1,048/4,232	1,466/7,489



Albani	18%	0.82 [0.61-1.06]	60/211	172/605
Synolaki	24%	0.76 [0.49-1.18]	21/98	60/214
Alamdari	55%	0.45 [0.25-0.83]	54/427	9/32
Heberto	54%	0.46 [0.19-0.97]	139 (n)	115 (n)
Lauriola	74%	0.27 [0.17-0.41]	102/297	35/63
Serrano	43%	0.57 [0.28-1.18]	6/14	6/8
Ulrich (RCT)	-6%	1.06 [0.38-2.98]	7/67	6/61
Shoaibi	15%	0.85 [0.79-0.91]	686/5,047	3,923/24,404
Ayerbe	52%	0.48 [0.37-0.62]	237/1,857	49/162
Nachega	28%	0.72 [0.49-1.06]	69/630	28/96
Ader (RCT)	6%	0.94 [0.43-2.05]	11/145	12/148
Soto-Becerra	18%	0.82 [0.76-0.89]	346/692	1,606/2,630
Aparisi	63%	0.37 [0.27-0.50]	122/605	27/49
Annie	4%	0.96 [0.65-1.37]	48/367	50/367
SOLIDARITY (RCT)	-19%	1.19 [0.89-1.59]	104/947	84/906
Guisado-Vasco	20%	0.80 [0.47-1.26]	127/558	14/49
Solh	-18%	1.18 [0.93-1.51]	131/265	134/378
Ñamendys-Silva	32%	0.68 [0.48-0.96]	24/54	42/64
Dubee (RCT)	46%	0.54 [0.21-1.42]	6/124	11/123
Lano	33%	0.67 [0.28-1.31]	56 (n)	66 (n)
Coll	46%	0.54 [0.41-0.72]	55/307	108/328
Frontera (PSM)	37%	0.63 [0.44-0.91]	121/1,006	424/2,467
Tehrani	13%	0.87 [0.54-1.40]	16/65	54/190
Salazar	-37%	1.37 [0.77-2.42]	12/92	80/811
Rodriguez-Nava	-6%	1.06 [0.72-1.56]	22/65	79/248
Maldonado	91%	0.09 [0.02-0.50]	1/11	1/1
Núñez-Gil	8%	0.92 [0.87-0.94]	200/686	100/268
Self (RCT)	-6%	1.06 [0.57-1.87]	25/241	25/236
Rodriguez	59%	0.41 [0.13-1.31]	8/39	2/4
Águila-Gordo	67%	0.33 [0.09-1.24]	151/346	47/70
Sheshah	80%	0.20 [0.09-0.45]	267 (n)	33 (n)
Boari	55%	0.45 [0.30-0.68]	41/202	25/56
Budhiraja	65%	0.35 [0.24-0.50]	69/834	34/142
Falcone (PSM)	65%	0.35 [0.07-1.73]	40/238	30/77
Qin	34%	0.66 [0.22-2.00]	3/43	75/706
Burdick	-59%	1.59 [0.89-2.83]	142 (n)	148 (n)
van Halem	32%	0.68 [0.47-1.00]	34/164	47/155
Rodriguez-Gonzalez	23%	0.77 [0.51-1.17]	251/1,148	17/60
Lambermont	32%	0.68 [0.48-0.96]	97/225	14/22
Abdulrahman (PSM)	17%	0.83 [0.26-2.69]	5/223	6/223
Modrák	59%	0.41 [0.19-1.03]	108 (n)	105 (n)
Ozturk	44%	0.56 [0.28-1.13]	165/1,127	6/23
Guglielmetti	35%	0.65 [0.33-1.30]	181 (n)	37 (n)
Bielza	22%	0.78 [0.59-1.05]	33/91	249/539
Naseem	33%	0.67 [0.30-1.53]	77 (n)	1,137 (n)
Orioli	13%	0.87 [0.26-2.94]	8/55	3/18
De Luna	-105%	2.05 [0.29-14.6]	15/132	1/18
Signes-Costa	47%	0.53 [0.37-0.75]	4,854 (n)	993 (n)
Matangila	55%	0.45 [0.07-1.27]	25/147	8/13
Cangiano	73%	0.27 [0.12-0.61]	5/33	37/65
Taccone	25%	0.75 [0.58-0.95]	449/1,308	183/439
Chari	33%	0.67 [0.37-1.22]	8/29	195/473
Vernaz (PSM)	15%	0.85 [0.42-1.70]	12/93	16/105
Texeira	-79%	1.79 [0.95-3.38]	17/65	14/96
Psevdos	-63%	1.63 [0.55-4.84]	17/52	3/15
Sands	-70%	1.70 [1.18-2.42]	101/973	56/696
Lotfy	-25%	1.25 [0.39-3.96]	6/99	5/103
Sarfaraz	-45%	1.45 [0.98-2.15]	40/94	27/92
Yegerov	95%	0.05 [0.00-0.75]	0/23	20/1,049
Di Castelnuovo	40%	0.60 [0.50-0.70]	3,270 (n)	1,000 (n)
Roig	16%	0.84 [0.49-1.44]	33/67	7/12
Ubaldo	18%	0.82 [0.52-1.28]	17/25	5/6
Ouedraogo	33%	0.67 [0.28-1.62]	397 (n)	59 (n)
Hernandez-C.. (RCT)	12%	0.88 [0.51-1.53]	106 (n)	108 (n)
Thompson (RCT)	-6%	1.06 [0.57-1.87]	25/241	25/236
Lora-Tamayo	50%	0.50 [0.44-0.56]	7,192 (n)	1,361 (n)
Awad	-19%	1.19 [0.84-1.70]	56/188	37/148
Lamback	9%	0.91 [0.41-2.00]	11/101	11/92
Gonzalez (RCT)	63%	0.37 [0.08-1.73]	2/33	6/37
Salvador	33%	0.67 [0.40-1.03]	28/121	58/124
Martin-Vicente	59%	0.41 [0.18-0.94]	37/91	1/1
Stewart	1%	0.99 [0.73-1.35]	66/578	188/1,243
Stewart	-130%	2.30 [1.49-3.54]	32/108	33/256



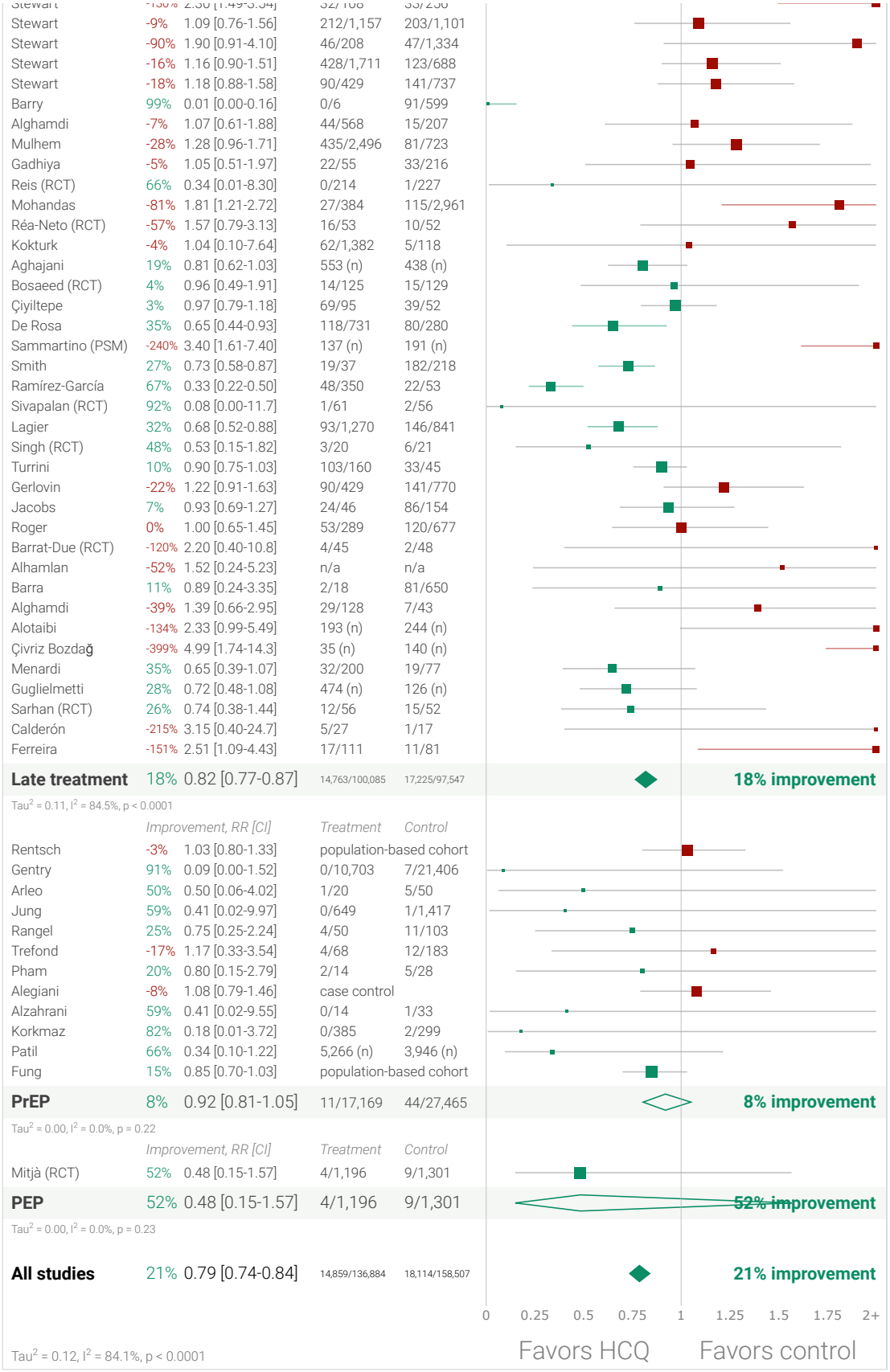


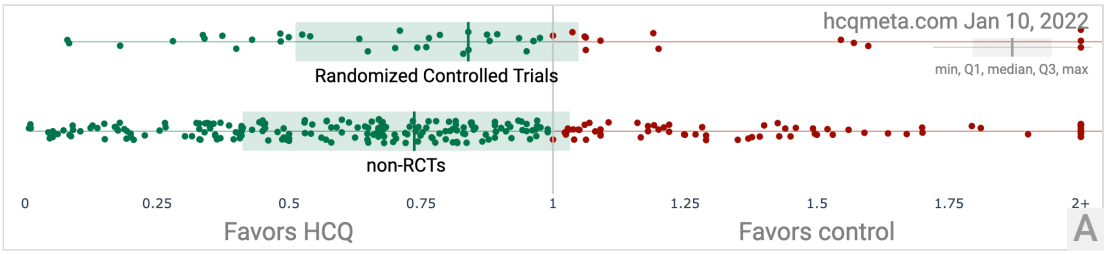
Figure 6. *Random effects meta-analysis for mortality results only. (ES) indicates the early treatment subset of a study (these are not included in the overall results).*

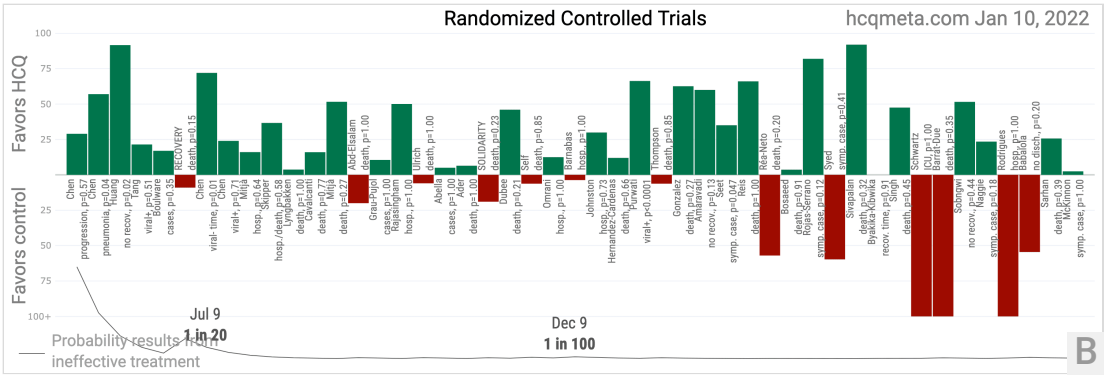
Figure 7. *Random effects meta-analysis for hospitalization results only.*

Randomized Controlled Trials (RCTs)

Randomized Controlled Trials (RCTs) minimize one source of bias and can provide a higher level of evidence. Results restricted to RCTs are shown in Figure 8, Figure 9, and Table 2. Even with the small number of RCTs to date, they confirm efficacy for early treatment. While late treatment RCTs are dominated by the very late stage and large RECOVERY/SOLIDARITY trials, prophylaxis and early treatment studies show 28% improvement in random effects meta-analysis, RR 0.72 [0.60-0.87], p = 0.00062. Early treatment RCTs show 46% improvement, RR 0.54 [0.35-0.84], p = 0.0058.

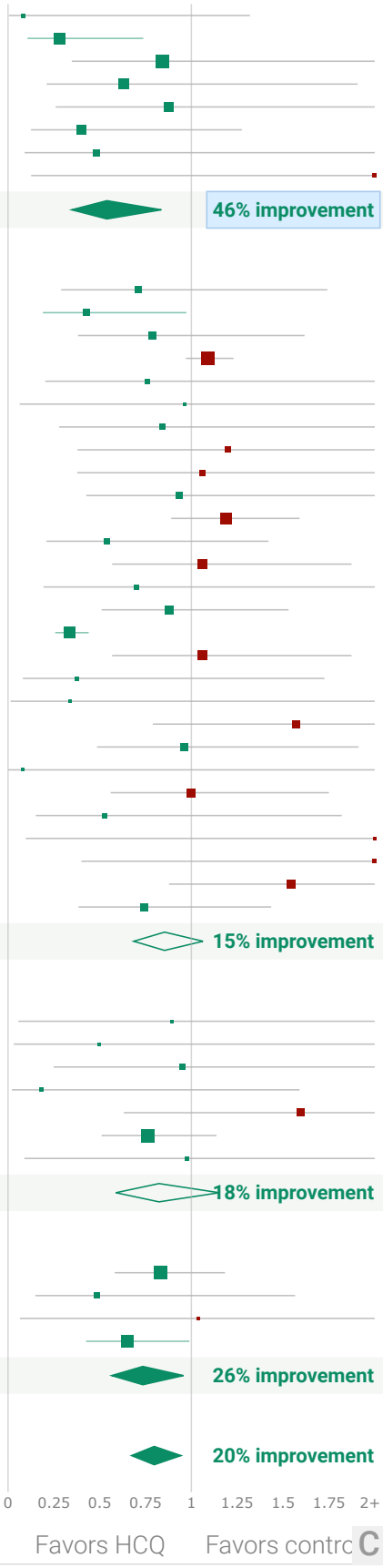
Evidence supports incorporating non-RCT studies. ***[Concato]*** find that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. ***[Anglemyer]*** summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. ***[Lee]*** shows that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Limitations in an RCT can easily outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet survey bias could easily have a greater effect on results. Ethical issues may prevent running RCTs for known effective treatments. For more on the problems with RCTs see ***[Deaton, Nichol]***.


hcqmeta.com Jan 10, 2022
Randomized Controlled Trials
min, Q1, median, Q3, max
non-RCTs
0
0.25
0.5
0.75
1
1.25
1.5
1.75
2+
Favors HCQ
Favors control
A


Randomized Controlled Trials
hcqmeta.com Jan 10, 2022
Favors HCQ
Favors control
100
75
50
25
Jul 9
1 in 20
Dec 9
1 in 100
Probability results from ineffective treatment
B

All 47 hydroxychloroquine COVID-19 RCTs

hcqmeta.com Jan 10, 2022



	Improvement	RR [CI]		Treatment	Control
Huang (RCT)	92%	0.08 [0.01-1.32]	no recov.	0/10	6/12
Chen (RCT)	72%	0.28 [0.11-0.74]	viral time	18 (n)	12 (n)
Mitjà (RCT)	16%	0.84 [0.35-2.03]	hosp.	8/136	11/157
Skipper (RCT)	37%	0.63 [0.21-1.91]	hosp./death	5/231	8/234
Omrani (RCT)	12%	0.88 [0.26-2.94]	hosp.	7/304	4/152
Amaravadi (RCT)	60%	0.40 [0.13-1.28]	no recov.	3/15	6/12
Sobngwi (RCT)	52%	0.48 [0.09-2.58]	no recov.	2/95	4/92
Rodrigues (RCT)	-200%	3.00 [0.13-71.6]	hosp.	1/42	0/42
Early treatment	46%	0.54 [0.35-0.84]		26/851	39/713

$Tau^2 = 0.00, I^2 = 0.0\%, p = 0.0058$

	Improvement	RR [CI]		Treatment	Control
Chen (RCT)	29%	0.71 [0.29-1.74]	progression	5/15	7/15
Chen (RCT)	57%	0.43 [0.19-0.97]	pneumonia	6/31	14/31
Tang (RCT)	21%	0.79 [0.38-1.62]	viral+	11/75	14/75
RECOVERY (RCT)	-9%	1.09 [0.97-1.23]	death	421/1,561	790/3,155
Chen (RCT)	24%	0.76 [0.20-2.84]	viral+	4/21	3/12
Lyngbakken (RCT)	4%	0.96 [0.06-14.6]	death	1/27	1/26
Cavalcanti (RCT)	16%	0.84 [0.28-2.53]	death	8/331	5/173
Abd-Elsalam (RCT)	-20%	1.20 [0.38-3.80]	death	6/97	5/97
Ulrich (RCT)	-6%	1.06 [0.38-2.98]	death	7/67	6/61
Ader (RCT)	6%	0.94 [0.43-2.05]	death	11/145	12/148
SOLIDARITY (RCT)	-19%	1.19 [0.89-1.59]	death	104/947	84/906
Dubee (RCT)	46%	0.54 [0.21-1.42]	death	6/124	11/123
Self (RCT)	-6%	1.06 [0.57-1.87]	death	25/241	25/236
Johnston (RCT)	30%	0.70 [0.19-2.54]	hosp.	5/148	4/83
Hernandez-C.. (RCT)	12%	0.88 [0.51-1.53]	death	106 (n)	108 (n)
Purwati (RCT)	66%	0.34 [0.26-0.44]	viral+	38/121	111/119
Thompson (RCT)	-6%	1.06 [0.57-1.87]	death	25/241	25/236
Gonzalez (RCT)	63%	0.37 [0.08-1.73]	death	2/33	6/37
Reis (RCT)	66%	0.34 [0.01-8.30]	death	0/214	1/227
Réa-Neto (RCT)	-57%	1.57 [0.79-3.13]	death	16/53	10/52
Bosaeed (RCT)	4%	0.96 [0.49-1.91]	death	14/125	15/129
Sivapalan (RCT)	92%	0.08 [0.00-11.7]	death	1/61	2/56
Byakika-Kib.. (RCT)	0%	1.00 [0.56-1.75]	recov. time	36 (n)	29 (n)
Singh (RCT)	48%	0.53 [0.15-1.82]	death	3/20	6/21
Schwartz (RCT)	-133%	2.33 [0.10-56.1]	ICU	1/111	0/37
Barrat-Due (RCT)	-120%	2.20 [0.40-10.8]	death	4/45	2/48
Babalola (RCT)	-55%	1.55 [0.88-2.72]	no disch.	17/30	11/30
Sarhan (RCT)	26%	0.74 [0.38-1.44]	death	12/56	15/52
Late treatment	15%	0.85 [0.69-1.06]		753/5,082	1,185/6,322

$Tau^2 = 0.16, I^2 = 69.2\%, p = 0.16$

	Improvement	RR [CI]		Treatment	Control
Grau-Pujol (RCT)	11%	0.89 [0.06-14.2]	cases	1/142	1/127
Rajasingham (RCT)	50%	0.50 [0.03-7.97]	hosp.	1/989	1/494
Abella (RCT)	5%	0.95 [0.25-3.63]	cases	4/64	4/61
Rojas-Serrano (RCT)	82%	0.18 [0.02-1.59]	symp. case	1/62	6/65
Syed (RCT)	-60%	1.60 [0.63-4.04]	symp. case	10/48	6/46
Naggie (RCT)	24%	0.76 [0.51-1.14]	symp. case	41/683	53/676
McKinnon (RCT)	2%	0.98 [0.09-10.7]	symp. case	2/365	1/178
PrEP	18%	0.82 [0.59-1.15]		60/2,353	72/1,647

$Tau^2 = 0.00, I^2 = 0.0\%, p = 0.26$

	Improvement	RR [CI]		Treatment	Control
Boulware (RCT)	17%	0.83 [0.58-1.18]	cases	49/414	58/407
Mitjà (RCT)	52%	0.48 [0.15-1.57]	death	4/1,196	9/1,301
Barnabas (RCT)	-4%	1.04 [0.07-16.5]	hosp.	1/407	1/422
Seet (RCT)	35%	0.65 [0.43-0.99]	symp. case	29/432	64/619
PEP	26%	0.74 [0.57-0.96]		83/2,449	132/2,749

$Tau^2 = 0.00, I^2 = 0.0\%, p = 0.022$

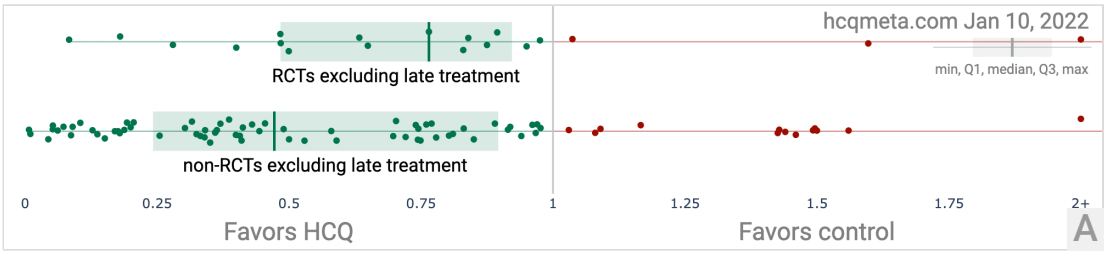
All studies	20%	0.80 [0.67-0.94]		922/10,735	1,428/11,431

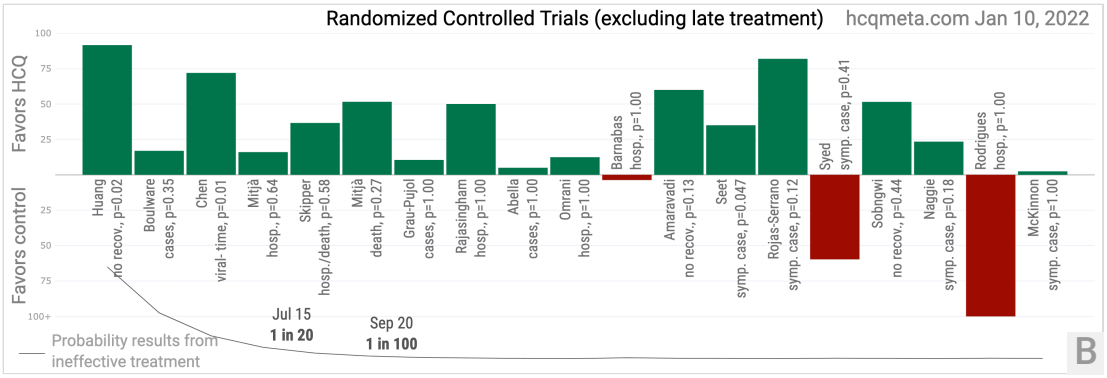
$Tau^2 = 0.12, I^2 = 58.0\%, p = 0.0084$

Effect extraction pre-specified, see appendix

C

Figure 8. *Randomized Controlled Trials. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.* ***A.*** *Scatter plot of all effects comparing RCTs to non-RCTs.* ***B.*** *Chronological history of all reported effects.*





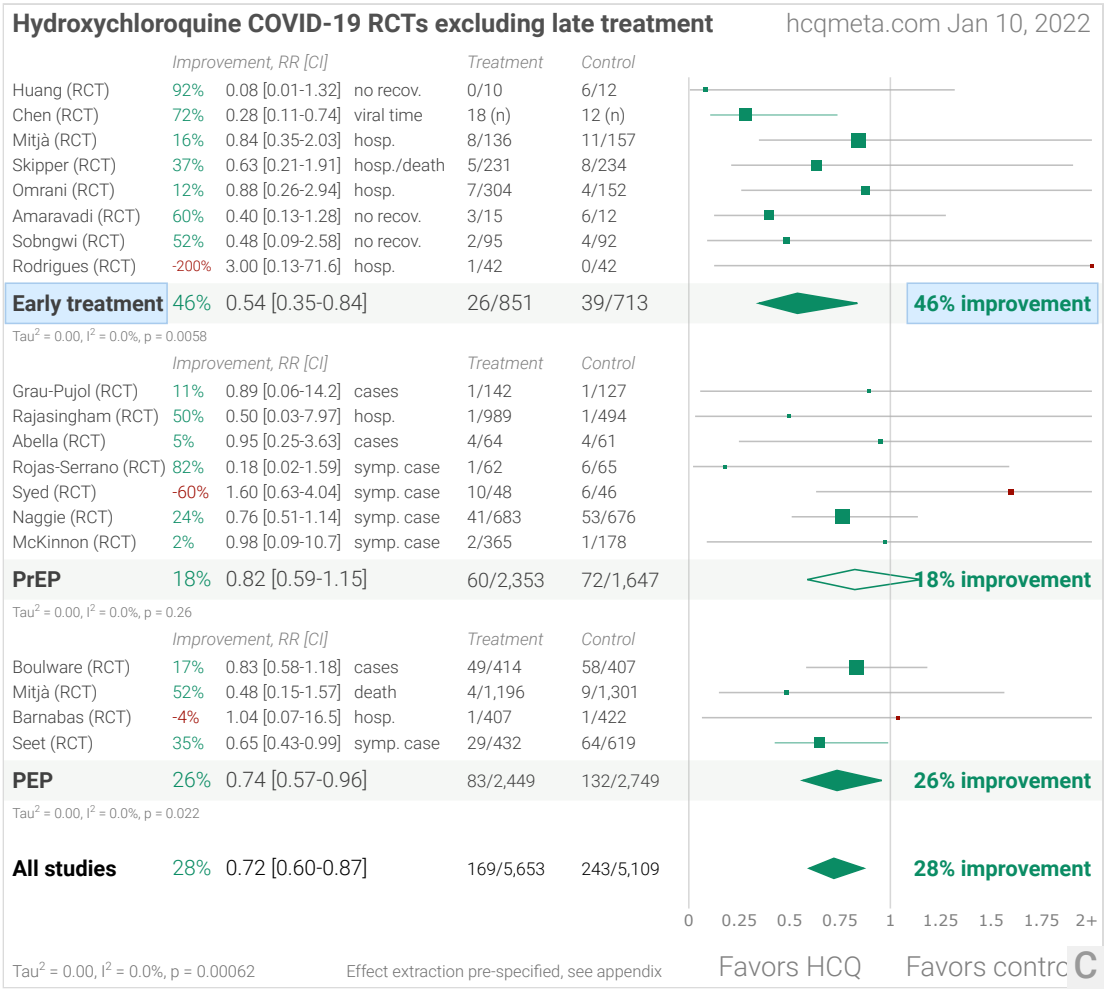


Figure 9. *RCTs excluding late treatment. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.* ***A.*** *Scatter plot of all effects comparing RCTs to non-RCTs.* ***B.*** *Chronological history of all reported effects.* ***C.*** *Random effects meta-analysis.*

Treatment time	Number of studies reporting positive results	Total number of studies	Percentage of studies reporting positive results	Probability of an equal or greater percentage of positive results from an ineffective treatment	Random effects meta-analysis results
Randomized Controlled Trials	33	47	70.2%	1 in 252	20% improvement RR 0.80 [0.67-0.94] p = 0.0084
Randomized Controlled Trials (excluding late treatment)	16	19	84.2%	1 in 452	28% improvement RR 0.72 [0.60-0.87] p = 0.00062

Table 2. *Summary of RCT results.*

Analysis with Exclusions

Many meta-analyses for HCQ have been written, most of which have become somewhat obselete due to the continuing stream of more recent studies. Recent analyses with positive conclusions include ***[IHU Marseille]*** which considers significant bias from an understanding of each trial, and ***[Garcia-Albeniz, Ladapo, Prodromos]*** which focus on early or prophylactic use studies.

Meta analyses reporting negative conclusions focus on late treatment studies, tend to disregard treatment delay, tend to follow formulaic evaluations which overlook major issues with various studies, and end up with weighting disproportionate to a reasoned analysis of each study's contribution. For example, ***[Axfors]*** assigns 87% weight to a single trial, the RECOVERY trial ***[RECOVERY]***, thereby producing the same result. However, the RECOVERY trial may be the most biased of the studies they included, due to the excessive dosage used, close to the level shown to be very dangerous in ***[Borba]*** (OR 2.8), and with extremely sick late stage patients (60% requiring oxygen, 17% ventilation/ECMO, and a very high mortality rate in both arms). There is little reason to suggest that the results from this trial are applicable to more typical dosages or to earlier treatment (10/22: the second version of this study released 10/22 assigns 74% to RECOVERY and 15% to SOLIDARITY ***[SOLIDARITY]***, which is the only other trial using a similar excessive dosage).

We include all studies in the main analysis, however there are major issues with several studies that could significantly alter the results. Here, we present an analysis excluding studies with significant issues, including indication of significant unadjusted group differences or confouding by indication, extremely late stage usage >14 days post symptoms or >50% on oxygen at baseline, very minimal detail provided, excessive dosages which have been shown to be dangerous, significant issues with adjustments that could reasonably make substantial differences, and reliance on PCR which may be inaccurate and less indicative of severity than symptoms. The aim here is not to exclude studies on technicalities, but to exclude studies that clearly have major issues that may significantly change the outcome. We welcome feedback on improvements or corrections to this. The studies excluded are as follows, and the resulting forest plot is shown in Figure 10.

[Ader], very late stage, >50% on oxygen/ventilation at baseline.

[Alamdari], substantial unadjusted confounding by indication likely.

[Albani], substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Alghamdi], unadjusted results with no group details, very late stage, ICU patients.

[Alghamdi (B)], confounding by indication is likely and adjustments do not consider COVID-19 severity.

[Alhamlan], substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Annie], confounding by indication is likely and adjustments do not consider COVID-19 severity.

[Aparisi], unadjusted results with no group details.

[Awad], substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.

[Barbosa], excessive unadjusted differences between groups.

[Barra], unadjusted results with no group details.

[Bielza], unadjusted results with no group details.

[Boari], unadjusted results with no group details.

[Bosaeed], very late stage, >50% on oxygen/ventilation at baseline.

[Budhiraja], excessive unadjusted differences between groups.

[Cassione], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Chari], unadjusted results with no group details.

[Chechter], unadjusted results with no group details.

[Choi], excessive unadjusted differences between groups.

[Coll], unadjusted results with no group details.

[Cravedi], substantial unadjusted confounding by indication likely.

[de la Iglesia], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[De Luna], unadjusted results with no group details, substantial unadjusted confounding by indication likely.

[Fitzgerald], not fully adjusting for the baseline risk differences within systemic autoimmune patients.

[Fried], excessive unadjusted differences between groups, substantial unadjusted confounding by indication likely.

[Fung], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Gadhiya], substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.

[Gautret], excessive unadjusted differences between groups, results only for PCR status which may be significantly different to symptoms.

[Geleris], significant issues found with adjustments.

[Gendebien], not fully adjusting for the baseline risk differences within systemic autoimmune patients.

[Gendelman], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Gianfrancesco], not fully adjusting for the baseline risk differences within systemic autoimmune patients.

[Goldman], unadjusted results with no group details.

[Gupta], very late stage, >50% on oxygen/ventilation at baseline.

[Hraiech], very late stage, ICU patients.

[Huang], significant unadjusted confounding possible.

[Huh], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Huh (B)], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Izoulet], excessive unadjusted differences between groups.

[Jacobs], unadjusted results with no group details, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Kamran], excessive unadjusted differences between groups.

[Kamstrup], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Kelly], substantial unadjusted confounding by indication likely.

[Konig], not fully adjusting for the baseline risk differences within systemic autoimmune patients.

[Krishnan], unadjusted results with no group details.

[Kuderer], substantial unadjusted confounding by indication likely.

[Küçükakkaş], minimal details of groups provided.

[Lamback], substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Laplana], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Lecronier], very late stage, >50% on oxygen/ventilation at baseline.

[Lotfy], substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.

[Luo], substantial unadjusted confounding by indication likely.

[Macias], not fully adjusting for the baseline risk differences within systemic autoimmune patients.

[Maldonado], treatment or control group size extremely small.

[Martin-Vicente], unadjusted results with no group details, treatment or control group size extremely small.

[McGrail], excessive unadjusted differences between groups.

[Menardi], excessive unadjusted differences between groups, substantial unadjusted confounding by indication likely.

[Mitchell], excessive unadjusted differences between groups.

[Mohandas], substantial unadjusted confounding by indication likely, unadjusted results with no group details, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Mulhem], substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Pasquini], unadjusted results with no group details.

[Peters], excessive unadjusted differences between groups.

[Psevdos], unadjusted results with no group details, no treatment details, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.

[Qin], unadjusted results with no group details.

[Ramírez-García], excessive unadjusted differences between groups, substantial unadjusted confounding by indication likely.

[Rangel], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Rao], unadjusted results with minimal group details.

[RECOVERY], excessive dosage in late stage patients, results do not apply to typical dosages.

[Rentsch], not fully adjusting for the baseline risk differences within systemic autoimmune patients, medication adherence unknown and may significantly change results.

[Rodriguez], unadjusted results with no group details.

[Rodriguez-Nava], substantial unadjusted confounding by indication likely, excessive unadjusted differences between groups, unadjusted results with no group details.

[Roger], substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Roig], unadjusted results with no group details.

[Roomi], substantial unadjusted confounding by indication likely.

[Roy], no serious outcomes reported and fast recovery in treatment and control groups, there is little room for a treatment to improve results.

[Saib], substantial unadjusted confounding by indication likely.

[Salazar], substantial unadjusted confounding by indication likely, unadjusted results with no group details.

[Saleemi], substantial unadjusted confounding by indication likely.

[Salvarani], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Samajdar], minimal details provided, unadjusted results with no group details, results may be significantly affected by survey bias.

[Sammartino], substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Sands], includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons, substantial unadjusted confounding by indication likely.

[Sarfaraz], substantial unadjusted confounding by indication likely, significant unadjusted confounding possible, unadjusted results with no group details.

[Sarhan], very late stage, >50% on oxygen/ventilation at baseline, significant unadjusted differences between groups.

[Sbidian], significant issues found with adjustments.

[Shoaibi], unadjusted results with no group details.

[Singer], not fully adjusting for the baseline risk differences within systemic autoimmune patients.

[Singh], confounding by indication is likely and adjustments do not consider COVID-19 severity.

[Smith], immortal time bias may significantly affect results.

[Solh], very late stage, >50% on oxygen/ventilation at baseline, substantial unadjusted confounding by indication likely.

[SOLIDARITY], excessive dosage in late stage patients, results do not apply to typical dosages, very late stage, >50% on oxygen/ventilation at baseline.

[Sosa-García], very late stage, >50% on oxygen/ventilation at baseline, substantial unadjusted confounding by indication likely.

[Soto-Becerra], substantial unadjusted confounding by indication likely, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Stewart], substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Stewart (B)], substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Stewart (C)], substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Stewart (D)], substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Stewart (E)], substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Stewart (F)], substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Stewart (G)], substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Tehrani], substantial unadjusted confounding by indication likely, unadjusted results with no group details.

[Texeira], unadjusted results with no group details, no treatment details, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.

[Trefond], not fully adjusting for the different baseline risk of systemic autoimmune patients, significant unadjusted confounding possible, excessive unadjusted differences between groups.

[Ubaldo], substantial unadjusted confounding by indication likely, very late stage, ICU patients, unadjusted results with no group details.

[Ulrich], very late stage, >50% on oxygen/ventilation at baseline.

[Vernaz], substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.

[Vivanco-Hidalgo], not fully adjusting for the different baseline risk of systemic autoimmune patients.

[Wang], confounding by indication is likely and adjustments do not consider COVID-19 severity.

[Xia], minimal details provided.

[Yegerov], unadjusted results with no group details.

[Çivriz Bozdağ], substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

[Çiyiltepe], treatment group only includes patients where treatment failed resulting in ICU admission.

194 hydroxychloroquine COVID-19 studies after exclusions

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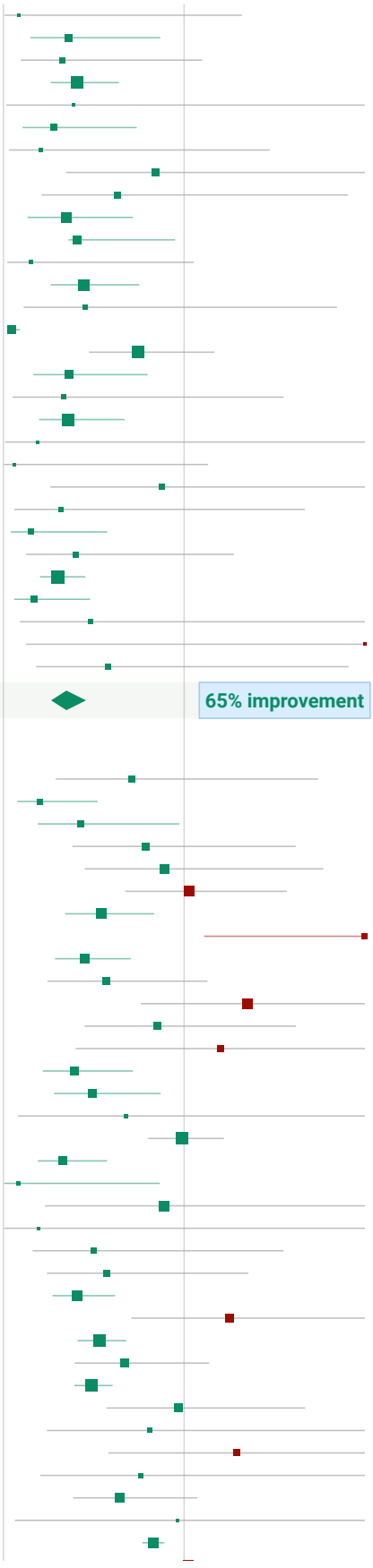
	Improvement, RR [CI]			Treatment	Control
Huang (RCT)	92%	0.08 [0.01-1.32]	no recov.	0/10	6/12
Esper	64%	0.36 [0.15-0.87]	hosp.	8/412	12/224
Ashraf	68%	0.32 [0.10-1.10]	death	10/77	2/5
Huang (ES)	59%	0.41 [0.26-0.64]	viral time	32 (n)	37 (n)
Guérin	61%	0.39 [0.02-9.06]	death	0/20	1/34
Chen (RCT)	72%	0.28 [0.11-0.74]	viral time	18 (n)	12 (n)
Derwand	79%	0.21 [0.03-1.47]	death	1/141	13/377
Mitjà (RCT)	16%	0.84 [0.35-2.03]	hosp.	8/136	11/157
Skipper (RCT)	37%	0.63 [0.21-1.91]	hosp./death	5/231	8/234
Hong	65%	0.35 [0.13-0.72]	viral+	42 (n)	48 (n)
Bernabeu-Wittel	59%	0.41 [0.36-0.95]	death	189 (n)	83 (n)
Yu (ES)	85%	0.15 [0.02-1.05]	death	1/73	238/2,604
Ly	56%	0.44 [0.26-0.75]	death	18/116	29/110
Ip	55%	0.45 [0.11-1.85]	death	2/97	44/970
Heras	96%	0.04 [0.02-0.09]	death	8/70	16/30
Kirenga	26%	0.74 [0.47-1.17]	recov. time	29 (n)	27 (n)
Sulaiman	64%	0.36 [0.17-0.80]	death	7/1,817	54/3,724
Guisado-Vasco (ES)	67%	0.33 [0.05-1.55]	death	2/65	139/542
Szente Fonseca	64%	0.36 [0.20-0.67]	hosp.	25/175	89/542
Cadegiani	81%	0.19 [0.01-3.88]	death	0/159	2/137
Simova	94%	0.06 [0.00-1.13]	hosp.	0/33	2/5
Omrani (RCT)	12%	0.88 [0.26-2.94]	hosp.	7/304	4/152
Agusti	68%	0.32 [0.06-1.67]	progression	2/87	4/55
Su	85%	0.15 [0.04-0.57]	progression	261 (n)	355 (n)
Amaravadi (RCT)	60%	0.40 [0.13-1.28]	no recov.	3/15	6/12
Mokhtari	70%	0.30 [0.20-0.45]	death	27/7,295	287/21,464
Million	83%	0.17 [0.06-0.48]	death	5/8,315	11/2,114
Sobngwi (RCT)	52%	0.48 [0.09-2.58]	no recov.	2/95	4/92
Rodrigues (RCT)	-200%	3.00 [0.13-71.6]	hosp.	1/42	0/42
Sawanpanyalert	42%	0.58 [0.18-1.91]	progression	n/a	n/a
Early treatment	65%	0.35 [0.27-0.45]		142/20,356	982/34,200

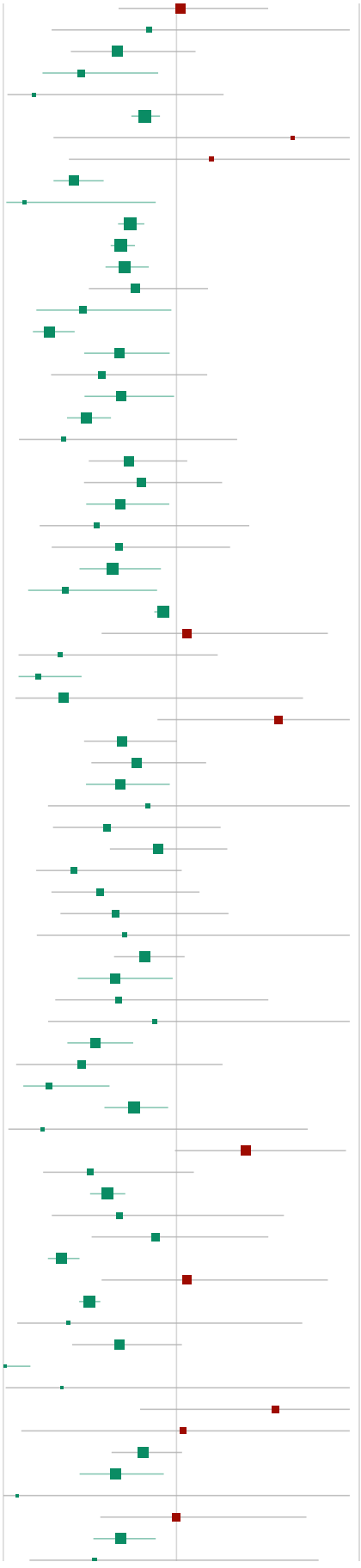
65% improvement

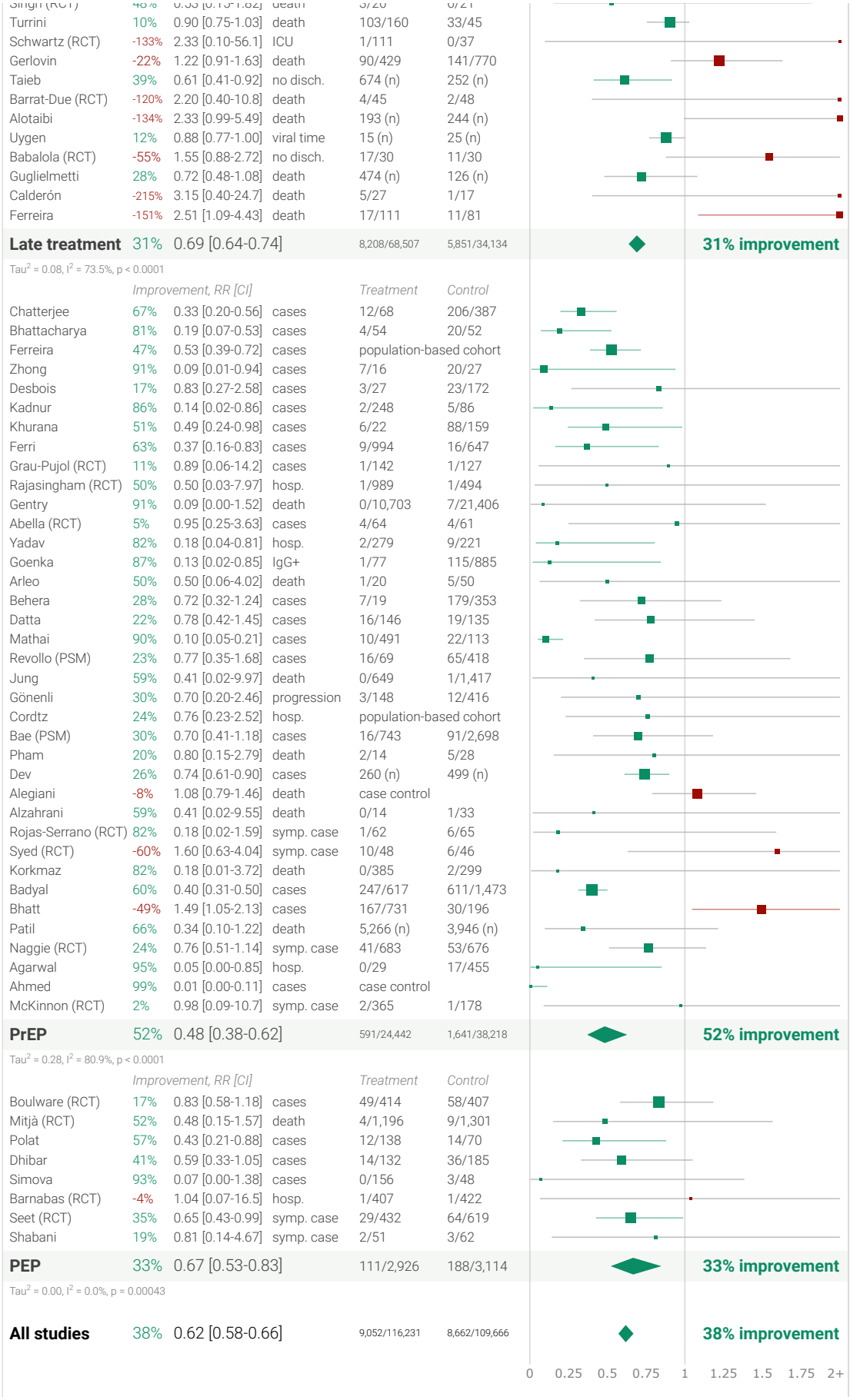
$Tau^2 = 0.20$, $I^2 = 51.7\%$, $p < 0.0001$

	Improvement, RR [CI]			Treatment	Control
Chen (RCT)	29%	0.71 [0.29-1.74]	progression	5/15	7/15
Zhong	80%	0.20 [0.08-0.52]	viral+	5/115	17/82
Chen (RCT)	57%	0.43 [0.19-0.97]	pneumonia	6/31	14/31
Tang (RCT)	21%	0.79 [0.38-1.62]	viral+	11/75	14/75
Magagnoli	11%	0.89 [0.45-1.77]	death	39/148	18/163
Auld	-3%	1.03 [0.67-1.57]	death	33/114	29/103
Sánchez-Álvarez	46%	0.54 [0.34-0.84]	death	322 (n)	53 (n)
Mallat	-203%	3.03 [1.11-7.69]	viral time	23 (n)	11 (n)
Membrillo de Nov..	55%	0.45 [0.29-0.71]	death	27/123	21/43
Alberici	43%	0.57 [0.24-1.13]	death	17/72	9/22
Rosenberg	-35%	1.35 [0.76-2.40]	death	189/735	28/221
Shabrawishi	15%	0.85 [0.45-1.62]	viral+	12/45	15/48
Mahévas	-20%	1.20 [0.40-3.30]	death	9/84	8/89
Yu	60%	0.40 [0.22-0.72]	death	9/48	238/502
Kim	51%	0.49 [0.28-0.87]	hosp. time	22/22	40/40
Luo	32%	0.68 [0.08-5.88]	death	19 (n)	264 (n)
Ip	1%	0.99 [0.80-1.22]	death	432/1,914	115/598
Huang	67%	0.33 [0.19-0.57]	viral time	197 (n)	176 (n)
Rogado	92%	0.08 [0.00-0.87]	death	1/8	7/9
Paccoud	11%	0.89 [0.23-3.47]	death	21/38	26/46
Faíco-Filho	81%	0.19 [0.00-8.66]	viral rate	34 (n)	32 (n)
Fontana	50%	0.50 [0.16-1.55]	death	4/12	2/3
Bousquet	43%	0.57 [0.24-1.36]	death	5/27	23/81
Lagier	59%	0.41 [0.27-0.62]	death	35/3,119	58/618
Komissarov	-25%	1.25 [0.71-2.21]	viral load	26/26	10/10
Mikami	47%	0.53 [0.41-0.68]	death	575/2,077	231/743
Martinez-Lopez	33%	0.67 [0.39-1.14]	death	47/148	9/19
Arshad	51%	0.49 [0.39-0.60]	death	162/1,202	108/409
An	3%	0.97 [0.57-1.67]	viral+	31/31	195/195
Rivera-Izquierdo	19%	0.81 [0.24-2.76]	death	215 (n)	23 (n)
Chen	-29%	1.29 [0.58-2.86]	viral+	16/28	4/9
Chen (RCT)	24%	0.76 [0.20-2.84]	viral+	4/21	3/12
Trullàs	36%	0.64 [0.39-1.07]	death	20/66	16/34
Lyngbakken (RCT)	4%	0.96 [0.06-14.6]	death	1/27	1/26
Bernaola	17%	0.83 [0.77-0.89]	death	236/1,498	28/147



Rivera	-2%	1.02 [0.67-1.53]	death	44/179	59/327
Cavalcanti (RCT)	16%	0.84 [0.28-2.53]	death	8/331	5/173
D'Arminio Monforte	34%	0.66 [0.39-1.11]	death	53/197	47/92
Davido	55%	0.45 [0.23-0.89]	int./hosp.	12/80	13/40
Yu	83%	0.17 [0.02-1.27]	progression	1/231	32/1,291
Berenguer	18%	0.82 [0.74-0.90]	death	681/2,618	438/1,377
Kalligeros	-67%	1.67 [0.29-9.36]	death	36 (n)	72 (n)
Abd-Elsalam (RCT)	-20%	1.20 [0.38-3.80]	death	6/97	5/97
Pinato	59%	0.41 [0.29-0.58]	death	30/182	181/446
Dubernet	88%	0.12 [0.02-0.88]	ICU	1/17	9/19
Gonzalez	27%	0.73 [0.66-0.81]	death	1,246/8,476	341/1,168
Catteau	32%	0.68 [0.62-0.76]	death	804/4,542	957/3,533
Di Castelnuovo	30%	0.70 [0.59-0.84]	death	386/2,634	90/817
Synolaki	24%	0.76 [0.49-1.18]	death	21/98	60/214
Heberto	54%	0.46 [0.19-0.97]	death	139 (n)	115 (n)
Lauriola	74%	0.27 [0.17-0.41]	death	102/297	35/63
Ashinyo	33%	0.67 [0.47-0.96]	hosp. time	61/61	61/61
Serrano	43%	0.57 [0.28-1.18]	death	6/14	6/8
Lammers	32%	0.68 [0.47-0.99]	death/ICU	30/189	101/498
Ayerbe	52%	0.48 [0.37-0.62]	death	237/1,857	49/162
Almazrou	65%	0.35 [0.09-1.35]	ventilation	3/95	6/66
Nachega	28%	0.72 [0.49-1.06]	death	69/630	28/96
Guisado-Vasco	20%	0.80 [0.47-1.26]	death	127/558	14/49
Ñamendys-Silva	32%	0.68 [0.48-0.96]	death	24/54	42/64
Dubee (RCT)	46%	0.54 [0.21-1.42]	death	6/124	11/123
Lano	33%	0.67 [0.28-1.31]	death	56 (n)	66 (n)
Frontera (PSM)	37%	0.63 [0.44-0.91]	death	121/1,006	424/2,467
López	64%	0.36 [0.14-0.89]	progression	5/36	14/36
Núñez-Gil	8%	0.92 [0.87-0.94]	death	200/686	100/268
Self (RCT)	-6%	1.06 [0.57-1.87]	death	25/241	25/236
Águila-Gordo	67%	0.33 [0.09-1.24]	death	151/346	47/70
Sheshah	80%	0.20 [0.09-0.45]	death	267 (n)	33 (n)
Falcone (PSM)	65%	0.35 [0.07-1.73]	death	40/238	30/77
Burdick	-59%	1.59 [0.89-2.83]	death	142 (n)	148 (n)
van Halem	32%	0.68 [0.47-1.00]	death	34/164	47/155
Rodriguez-Gonzalez	23%	0.77 [0.51-1.17]	death	251/1,148	17/60
Lambermont	32%	0.68 [0.48-0.96]	death	97/225	14/22
Abdulrahman (PSM)	17%	0.83 [0.26-2.69]	death	5/223	6/223
Capsoni	40%	0.60 [0.29-1.25]	ventilation	12/40	6/12
Peng	11%	0.89 [0.62-1.29]	progression	29/453	256/3,567
Modrák	59%	0.41 [0.19-1.03]	death	108 (n)	105 (n)
Ozturk	44%	0.56 [0.28-1.13]	death	165/1,127	6/23
Guglielmetti	35%	0.65 [0.33-1.30]	death	181 (n)	37 (n)
Johnston (RCT)	30%	0.70 [0.19-2.54]	hosp.	5/148	4/83
Alqassieh	18%	0.82 [0.64-1.05]	hosp. time	63 (n)	68 (n)
Tan	35%	0.65 [0.43-0.98]	hosp. time	8 (n)	277 (n)
Naseem	33%	0.67 [0.30-1.53]	death	77 (n)	1,137 (n)
Orioli	13%	0.87 [0.26-2.94]	death	8/55	3/18
Signes-Costa	47%	0.53 [0.37-0.75]	death	4,854 (n)	993 (n)
Matangila	55%	0.45 [0.07-1.27]	death	25/147	8/13
Cangiano	73%	0.27 [0.12-0.61]	death	5/33	37/65
Taccone	25%	0.75 [0.58-0.95]	death	449/1,308	183/439
Güner	77%	0.23 [0.03-1.76]	ICU	604 (n)	100 (n)
Li	-40%	1.40 [0.99-1.98]	viral time	18 (n)	19 (n)
Li	50%	0.50 [0.23-1.10]	no disch.	14 (n)	14 (n)
Di Castelnuovo	40%	0.60 [0.50-0.70]	death	3,270 (n)	1,000 (n)
Ouedraogo	33%	0.67 [0.28-1.62]	death	397 (n)	59 (n)
Hernandez-C.. (RCT)	12%	0.88 [0.51-1.53]	death	106 (n)	108 (n)
Purwati (RCT)	66%	0.34 [0.26-0.44]	viral+	38/121	111/119
Thompson (RCT)	-6%	1.06 [0.57-1.87]	death	25/241	25/236
Lora-Tamayo	50%	0.50 [0.44-0.56]	death	7,192 (n)	1,361 (n)
Gonzalez (RCT)	63%	0.37 [0.08-1.73]	death	2/33	6/37
Salvador	33%	0.67 [0.40-1.03]	death	28/121	58/124
Barry	99%	0.01 [0.00-0.16]	death	0/6	91/599
Reis (RCT)	66%	0.34 [0.01-8.30]	death	0/214	1/227
Réa-Neto (RCT)	-57%	1.57 [0.79-3.13]	death	16/53	10/52
Kokturk	-4%	1.04 [0.10-7.64]	death	62/1,382	5/118
Aghajani	19%	0.81 [0.62-1.03]	death	553 (n)	438 (n)
De Rosa	35%	0.65 [0.44-0.93]	death	118/731	80/280
Sivapalan (RCT)	92%	0.08 [0.00-11.7]	death	1/61	2/56
Byakika-Kib.. (RCT)	0%	1.00 [0.56-1.75]	recov. time	36 (n)	29 (n)
Lagier	32%	0.68 [0.52-0.88]	death	93/1,270	146/841
Singh (RCT)	48%	0.53 [0.15-1.82]	death	3/20	6/21




Singh (RCT) 46% 0.53 [0.13-1.82] death 3/20 6/21
Turrini 10% 0.90 [0.75-1.03] death 103/160 33/45
Schwartz (RCT) -133% 2.33 [0.10-56.1] ICU 1/111 0/37
Gerlovin -22% 1.22 [0.91-1.63] death 90/429 141/770
Taieb 39% 0.61 [0.41-0.92] no disch. 674 (n) 252 (n)
Barrat-Due (RCT) -120% 2.20 [0.40-10.8] death 4/45 2/48
Alotaibi -134% 2.33 [0.99-5.49] death 193 (n) 244 (n)
Uygen 12% 0.88 [0.77-1.00] viral time 15 (n) 25 (n)
Babalola (RCT) -55% 1.55 [0.88-2.72] no disch. 17/30 11/30
Guglielmetti 28% 0.72 [0.48-1.08] death 474 (n) 126 (n)
Calderón -215% 3.15 [0.40-24.7] death 5/27 1/17
Ferreira -151% 2.51 [1.09-4.43] death 17/111 11/81
Late treatment 31% 0.69 [0.64-0.74] 8,208/68,507 5,851/34,134
31% improvement
Tau² = 0.08, I² = 73.5%, p < 0.0001
Improvement, RR [CI] Treatment Control
Chatterjee 67% 0.33 [0.20-0.56] cases 12/68 206/387
Bhattacharya 81% 0.19 [0.07-0.53] cases 4/54 20/52
Ferreira 47% 0.53 [0.39-0.72] cases population-based cohort
Zhong 91% 0.09 [0.01-0.94] cases 7/16 20/27
Desbois 17% 0.83 [0.27-2.58] cases 3/27 23/172
Kadnur 86% 0.14 [0.02-0.86] cases 2/248 5/86
Khurana 51% 0.49 [0.24-0.98] cases 6/22 88/159
Ferri 63% 0.37 [0.16-0.83] cases 9/994 16/647
Grau-Pujol (RCT) 11% 0.89 [0.06-14.2] cases 1/142 1/127
Rajasingham (RCT) 50% 0.50 [0.03-7.97] hosp. 1/989 1/494
Gentry 91% 0.09 [0.00-1.52] death 0/10,703 7/21,406
Abella (RCT) 5% 0.95 [0.25-3.63] cases 4/64 4/61
Yadav 82% 0.18 [0.04-0.81] hosp. 2/279 9/221
Goenka 87% 0.13 [0.02-0.85] IgG+ 1/77 115/885
Arleo 50% 0.50 [0.06-4.02] death 1/20 5/50
Behera 28% 0.72 [0.32-1.24] cases 7/19 179/353
Datta 22% 0.78 [0.42-1.45] cases 16/146 19/135
Mathai 90% 0.10 [0.05-0.21] cases 10/491 22/113
Revollo (PSM) 23% 0.77 [0.35-1.68] cases 16/69 65/418
Jung 59% 0.41 [0.02-9.97] death 0/649 1/1,417
Gönenli 30% 0.70 [0.20-2.46] progression 3/148 12/416
Cordtz 24% 0.76 [0.23-2.52] hosp. population-based cohort
Bae (PSM) 30% 0.70 [0.41-1.18] cases 16/743 91/2,698
Pham 20% 0.80 [0.15-2.79] death 2/14 5/28
Dev 26% 0.74 [0.61-0.90] cases 260 (n) 499 (n)
Alegiani -8% 1.08 [0.79-1.46] death case control
Alzahrani 59% 0.41 [0.02-9.55] death 0/14 1/33
Rojas-Serrano (RCT) 82% 0.18 [0.02-1.59] symp. case 1/62 6/65
Syed (RCT) -60% 1.60 [0.63-4.04] symp. case 10/48 6/46
Korkmaz 82% 0.18 [0.01-3.72] death 0/385 2/299
Badyal 60% 0.40 [0.31-0.50] cases 247/617 611/1,473
Bhatt -49% 1.49 [1.05-2.13] cases 167/731 30/196
Patil 66% 0.34 [0.10-1.22] death 5,266 (n) 3,946 (n)
Naggie (RCT) 24% 0.76 [0.51-1.14] symp. case 41/683 53/676
Agarwal 95% 0.05 [0.00-0.85] hosp. 0/29 17/455
Ahmed 99% 0.01 [0.00-0.11] cases case control
McKinnon (RCT) 2% 0.98 [0.09-10.7] symp. case 2/365 1/178
PrEP 52% 0.48 [0.38-0.62] 591/24,442 1,641/38,218
52% improvement
Tau² = 0.28, I² = 80.9%, p < 0.0001
Improvement, RR [CI] Treatment Control
Boulware (RCT) 17% 0.83 [0.58-1.18] cases 49/414 58/407
Mitjà (RCT) 52% 0.48 [0.15-1.57] death 4/1,196 9/1,301
Polat 57% 0.43 [0.21-0.88] cases 12/138 14/70
Dhibar 41% 0.59 [0.33-1.05] cases 14/132 36/185
Simova 93% 0.07 [0.00-1.38] cases 0/156 3/48
Barnabas (RCT) -4% 1.04 [0.07-16.5] hosp. 1/407 1/422
Seet (RCT) 35% 0.65 [0.43-0.99] symp. case 29/432 64/619
Shabani 19% 0.81 [0.14-4.67] symp. case 2/51 3/62
PEP 33% 0.67 [0.53-0.83] 111/2,926 188/3,114
33% improvement
Tau² = 0.00, I² = 0.0%, p = 0.00043
All studies 38% 0.62 [0.58-0.66] 9,052/116,231 8,662/109,666
38% improvement
0 0.25 0.5 0.75 1 1.25 1.5 1.75 2+

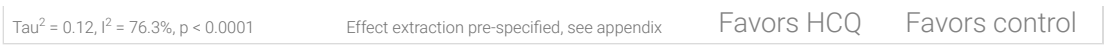


Figure 10. *Random effects meta-analysis excluding studies with significant issues. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. (ES) indicates the early treatment subset of a study (these are not included in the overall results).*

Heterogeneity

Heterogeneity in COVID-19 studies arises from many factors including:

Treatment delay. The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example a medication may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Figure 11 shows an example where efficacy declines as a function of treatment delay. Other medications might be beneficial for late stage complications, while early use may not be effective or may even be harmful.

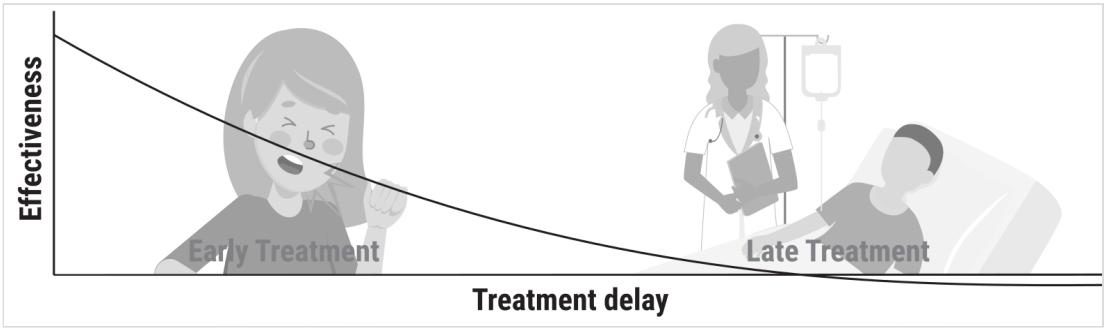


Figure 11. *Effectiveness may depend critically on treatment delay.*

Patient demographics. Details of the patient population including age and comorbidities may critically affect how well a treatment works. For example, many COVID-19 studies with relatively young low-comorbidity patients show all patients recovering quickly with or without treatment. In such cases, there is little room for an effective treatment to improve results.

Effect measured. Efficacy may differ significantly depending on the effect measured, for example a treatment may be very effective at reducing mortality, but less effective at minimizing cases or hospitalization. Or a treatment may have no effect on viral clearance while still being effective at reducing mortality.

Variants. There are thousands of different variants of SARS-CoV-2 and efficacy may depend critically on the distribution of variants encountered by the patients in a study.

Regimen. Effectiveness may depend strongly on the dosage and treatment regimen.

Treatments. The use of other treatments may significantly affect outcomes, including anything from other medications, supplements, or other kinds of treatment such as prone positioning.

The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though the treatment may be effective when used earlier.

In general, by combining heterogeneous studies, as all meta analyses do, we run the risk of obscuring an effect by including studies where the treatment is less effective, not effective, or harmful.

When including studies where a treatment is less effective we expect the estimated effect size to be lower than that for the optimal case. We do not *a priori* expect that pooling all studies will create a positive result for an effective treatment. Looking at all studies is valuable for providing an overview of all research, and important to avoid cherry-picking, but the resulting estimate does not apply to specific cases such as early treatment in high-risk populations.

HCQ studies vary widely in all the factors above. We find a significant effect based on treatment delay. Early treatment shows consistently positive results, while late treatment results are very mixed. Closer analysis may identify factors related to efficacy among this group, for example treatment may be more effective in certain popuations, or more fine-grained analysis of treatment delay may identify a point after which treatment is ineffective.

Discussion

Publication bias. Publishing is often biased towards positive results, which we would need to adjust for when analyzing the percentage of positive results. Studies that require less effort are considered to be more susceptible to publication bias. Prospective trials that involve significant effort are likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and the results may influence their decision to continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results.

For HCQ, 76.9% of prospective studies report positive effects, compared to 71.1% of retrospective studies, suggesting a bias toward publishing negative results. The median effect size for prospective studies is 27% improvement, compared to 24% for retrospective studies. Figure 12 shows a scatter plot of results for prospective and retrospective studies.

Figure 13 shows the results by region of the world, for all regions that have > 5 studies. Studies from North America are 2.7 times more likely to report negative results than studies from the rest of the world combined, 53.4% vs. 19.6%, two-tailed z test -5.56, p = 0.0000000264. ***[Berry]*** performed an independent analysis which also showed bias toward negative results for US-based research.

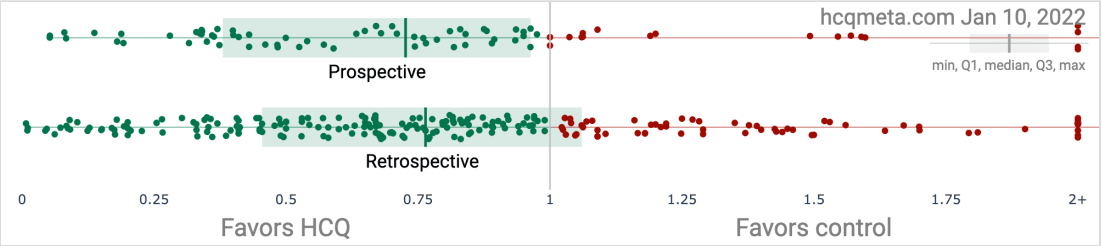


Figure 12. *Prospective vs. retrospective studies.*

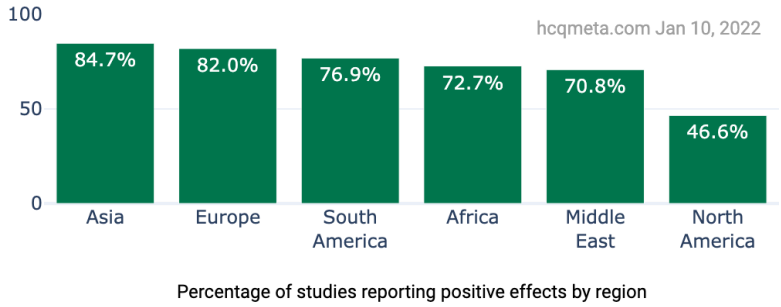


Figure 14. *Results by region.*

The lack of bias towards positive results is not very surprising. Both negative and positive results are very important given the current use of HCQ for COVID-19 around the world, evidence of which can be found in the studies analyzed here, government protocols, and news reports, for example *[AFP, AfricaFeeds, Africanews, Afrik.com, Al Arabia, Al-bab, Anadolu Agency, Anadolu Agency (B), Archyde, Barron's, Barron's (B), BBC, Belayneh, A., Bianet, CBS News, Challenge, Dr. Goldin, Efecto Cocuyo, Expats.cz, Face 2 Face Africa, Filipova, France 24, France 24 (B), Franceinfo, Global Times, Government of China, Government of India, Government of Venezuela, GulfInsider, Le Nouvel Afrik, LifeSiteNews, Medical World Nigeria, Medical Xpress, Medical Xpress (B), Middle East Eye, Ministerstva Zdravotnictví, Ministry of Health of Ukraine, Ministry of Health of Ukraine (B), Morocco World News, Mosaique Guinee, Nigeria News World, NPR News, Oneindia, Pan African Medical Journal, Parola, Pilot News, PledgeTimes, Pleno.News, Q Costa Rica, Rathi, Russian Government, Russian Government (B), Teller Report, The Africa Report, The Australian, The BL, The East African, The Guardian, The Indian Express, The Moscow Times, The North Africa Post, The Tico Times, Ukrinform, Vanguard, Voice of America]*.

We also note a bias towards publishing negative results by certain journals and press organizations, with scientists reporting difficulty publishing positive results *[Boulware, Meeus, Meneguesso]*. *[Meeus]*, for example, report that their paper with 4,000 patients reporting favourable outcomes for HCQ+AZ was rejected without peer review from the editors of four different journals.

Although 220 studies show positive results, The New York Times, for example, has only written articles for studies that claim HCQ is not effective *[The New York Times, The New York Times (B), The New York Times (C)]*. As of September 10, 2020, The New York Times still claims that there is clear evidence that HCQ is not effective for COVID-19 *[The New York Times (D)]*. As of October 9, 2020, the United States National Institutes of Health recommends against HCQ for both hospitalized and non-hospitalized patients *[United States National Institutes of Health]*.

Treatment details. We focus here on the question of whether HCQ is effective or not for COVID-19. Studies vary significantly in terms of treatment delay, treatment regimen, patients characteristics, and (for the pooled effects analysis) outcomes, as reflected in the high degree of heterogeneity. However, early treatment consistently shows benefits. 97% of early treatment studies report a positive effect, with an estimated reduction of 64% in the effect measured (death, hospitalization, etc.) in the random effects meta-analysis, RR 0.36 [0.28-0.46].

Negative Meta Analyses

Generally, it is easy to choose inclusion criteria and assign biased risk evaluations in order to produce any desired outcome in a meta analysis.

COVID-19 treatment studies have many sources of heterogeneity which affect the results, including treatment delay (time from infection or the onset of symptoms), patient population (age, comorbidities), the effect measured and details of the measurement, distribution of SARS-CoV-2 variants, dosage/regimen, and other treatments (anything from supplements, other medications, or other kinds of treatment like prone positioning).

If a treatment is effective early, there is no reason to expect it will also work late. Antivirals are typically only considered effective when used within a short timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective ***[McLean, Treanor]***. For HCQ, the overwhelming majority of trials involve treatment not only after 48 hours but after 5 days - results from these trials are not relevant to earlier usage.

Authors desiring to produce a negative outcome for HCQ need only focus on late treatment studies. For example, ***[Axfors]*** assigns 89% weight to the RECOVERY and SOLIDARITY trials, producing the same negative result. These trials used excessively high non-patient-customized dosage in very sick late stage patients, dosages comparable to those known to be harmful in that context ***[Borba]***. The results are not generalizable to typical dosage or treatment of earlier stage hospitalized patients, and certainly not applicable to early treatment, i.e., at first glance we can see that this meta analysis is of no relevance to early treatment.

This paper also does not appear to have been done very carefully. For example, authors include ***[Borba]*** which is assigned 97% weight for CQ. This study has no control group, comparing two different dosages of CQ, which is clear from the abstract of the study.

[Axfors] approximate early treatment with outpatient use, where they list 5 trials. This is misleading because authors ignore all outcomes other than mortality, and only one of the 5 trials has mortality events, so in reality only one trial is included. Table 1 shows the 5 trials, only one with mortality. The text says something different: "among the five studies on outpatients, there were three deaths, two occurring in the one trial of 491 relatively young patients with few comorbidities and one occurring in a small trial with 27 patients". We do not know what the missing 27 patient trial is, none of the 5 outpatient trials in Table 1 show 27 patients. There is an outpatient trial with 27 patients ***[Amaravadi]***, however that trial reports no mortality. It does appear in the meta analysis, but is reported as being an inpatient trial with zero mortality (in reality it was a remotely conducted trial of patients quarantined at home). The supplementary appendix has another different version for outpatient trials, with only 4 trials in Table S3 and Figure S2B (only one with mortality).

Therefore, of the 33 early treatment trials, authors have included data from only one, which contains only 1 death in each of the treatment and control groups. If we read the actual study ***[Skipper]***, we find that the death in the treatment group was a non-hospitalized patient, suggesting that the death was not caused by COVID-19, or at a minimum the patient did not receive standard care and the comparison here is therefore not valid.

Conclusion

HCQ is an effective treatment for COVID-19. Treatment is more effective when used early. Meta analysis using the most serious outcome reported shows 64% [54-72%] improvement for the 33 early treatment studies. Results are similar after exclusion based sensitivity analysis and after restriction to peer-reviewed studies. Restricting to the 8 RCTs shows 46% [16-65%] improvement, and restricting to the 13 mortality results shows 75% [60-84%] lower mortality. Very late stage treatment is not effective and may be harmful, especially when using excessive dosages.

Revisions

This paper is data driven, all graphs and numbers are dynamically generated. We will update the paper as new studies are released or with any corrections. Please submit updates and corrections at https://hcqmeta.com/.

1/10/2022: We updated ***[Syed]*** to the journal version.

12/23: We added ***[McKinnon]***.

12/14: We noted that the majority of the PrEP studies reporting negative effects are studies where all or most patients were autoimmune disorder patients ***[Crawford]***.

12/12: We added ***[Rao]***.

12/11: We added ***[Calderón]***.

12/5: We added ***[Ferreira]***.

12/4: We added ***[Ahmed]***.

12/4: We updated ***[Grau-Pujol]*** to the journal version.

11/18: We added ***[Samajdar]***.

11/7: We added ***[Chechter]***.

11/3: We added ***[Guglielmetti (B), Sarhan]***.

10/19: We added a summary plot for all results.

10/12: We added ***[Menardi]***.

10/10: We added *[Luo (B)]*.

10/4: We added *[Fung]*.

10/4: We added *[Babalola]*.

9/29: We corrected a display error causing some points to be missing in Figure 3.

9/27: We added *[Uygen]*, and updated *[Million]* to the journal version.

9/19: We added *[Alotaibi, Çivriz Bozdağ]*.

9/17: We added *[Çiyiltepe]*.

9/15: We added *[Agarwal]*.

9/14: We added *[Sawanpanyalert]*.

9/14: We added *[Mulhem]*.

9/12: We added *[Küçükakkaş]*.

9/9: We added *[Alhamlan]*.

9/7: Discussion updates.

8/28: We added *[Patil]*.

8/27: We added *[Rodrigues]*.

8/25: We added *[Naggie]*.

8/21: We added *[Gadhiya]*.

8/20: We corrected the event counts in *[Berenguer]*.

8/17: We added *[De Luna]*.

8/16: We added *[Turrini]*.

8/12: We added *[Shabani]*.

8/10: We added *[Rogado]*.

8/8: We added *[Di Castelnuovo]*.

8/7: We added *[Datta, Kadnur]*.

8/6: We added *[Yadav]*.

8/5: We added *[Bhatt]*.

8/4: We added *[Alghamdi]*.

8/3: We added *[Barra]*.

7/30: We updated *[Bosaeed]* to the journal version, and added *[Sobngwi]*.

7/19: We added analysis restricted to hospitalization results.

7/15: We added *[Jacobs]*.

7/14: We added *[Roger]*.

7/13: We added *[Barrat-Due]*.

7/11: We added *[Krishnan]*.

7/8: We updated *[Cadegiani]* to the journal version.

7/2: We added *[Taieb]*.

6/22: We added *[Schwartz]*.

6/21: We added *[Ramírez-García]*.

6/16: We added *[Saib]*.

6/12: We added *[Sivapalan]*.

6/8: We added *[Burdick, Singh (B)]*.

6/7: We added *[Badyal]*.

6/6: We added *[Lagier]*.

6/5: We added *[Thompson]*.

6/4: We added *[Byakika-Kibwika, Korkmaz]*.

6/2: We added *[Kamstrup, Smith]*.

5/28: We added *[Million]*.

5/17: We added *[Syed]*.

5/16: We added *[Rojas-Serrano]*. We corrected the group sizes for *[Skipper]*, and we excluded hospitalizations that were reported as not being related to COVID-19.

5/15: We added *[Sammartino]*.

5/14: We added more discussion of heterogeneity.

5/12: We added *[De Rosa]*.

5/10: We added additional information in the abstract.

5/8: We added *[Réa-Neto]*.

5/7: We added *[Kokturk]*.

5/3: We added an explanation of how some meta analyses produce negative results.

5/4: We added *[Aghajani]*.

5/1: We added *[Bosaeed]*.

4/29: We added *[Mohandas]*.

4/23: We added *[Reis]*.

4/20: We added *[Alegiani, Alzahrani]*.

4/14: We added *[Seet]*.

4/9: We updated *[Dubee]* to the journal version.

4/6: We added *[Mokhtari]*.

4/4: We updated *[Mitjà]* for 11 control hospitalizations. There is conflicting data, table S2 lists 12 control hospitalizations, while table 2 shows 11. A previous version of this paper also showed some values corresponding to 12 control hospitalizations in the abstract and table 2.

4/2: We added *[Salvarani]*.

4/1: We added *[Alghamdi (B)]*.

3/29: We added *[Barry]*.

3/28: We added *[Stewart]*.

3/27: We added *[Hraiech]*, and we corrected an error in effect extraction for *[Self]*.

3/24: We added *[Dev]*.

3/13: We added *[Roy]*.

3/9: We added *[Vivanco-Hidalgo]*.

3/8: We added *[Martin-Vicente]*.

3/7: We added *[Salvador]*.

3/5: We added *[Lotfy]*.

3/3: We added *[Pasquini]*.

3/2: We added *[Pham]*.

2/28: We added *[Rodriguez]*.

2/26: We added *[Amaravadi]*.

2/23: We added *[Gonzalez]*.

2/25: We added *[Bae]*.

2/20: We added *[Lamback]*.

2/18: We added *[Awad]*.

2/17: We added *[Purwati]*.

2/16: We added *[Albani]*.

2/15: We added *[Lora-Tamayo]*.

2/10: We added *[Roig, Ubaldo]*.

2/9: We added *[Ouedraogo]*.

2/7: We added *[Johnston]*.

2/6: We added *[Fitzgerald]*.

2/5: We added *[Hernandez-Cardenas]*.

2/2: We added *[Bernabeu-Wittel]*.

2/1: We added *[Trefond]*.

1/24: We added *[Desbois, Psevdos]*. We moved the analysis with exclusions and mortality analysis to the main text.

1/21: We added *[Li]*.

1/16: We added the effect measured for each study in the forest plots.

1/15: We updated *[Ip]* to the published version.

1/12: We added *[Li (B)]*.

1/11: We added *[Rangel]*.

1/9: We added *[Texeira, Yegerov]*.

1/7: We added direct links to the study details in the chronological plots.

1/6: We added direct links to the study details in the forest plots.

1/5: We added *[Sarfaraz]*.

1/4: We added *[Vernaz]*.

1/3: We added dosage information for early treatment studies.

1/2: We added the number of patients to the forest plots.

1/1/2021: We added *[Sands]*.

12/31: We added additional details about the studies in the appendix.

12/29: We added *[Güner, Salazar]*.

12/28: We added *[Auld, Cordtz]*.

12/27: We added the total number of authors and patients.

12/25: We added *[Chari]*.

12/24: We added *[Su]*.

12/23: We added *[Cangiano]*.

12/22: We added *[Taccone]*.

12/21: We added *[Matangila]*.

12/20: We added *[Gönenli, Huh]*.

12/17: We added *[Signes-Costa]*.

12/16: We added *[Alqassieh, Naseem, Orioli, Sosa-García, Tan]*.

12/15: We added *[Kalligeros, López]*.

12/14: We added *[Rivera-Izquierdo, Rodriguez-Nava]*.

12/13: We added *[Bielza]*.

12/11: We added *[Jung]*.

12/9: We added *[Agusti, Guglielmetti (B)]*.

12/8: We added *[Barnabas]*.

12/7: We added *[Maldonado]*.

12/4: We added *[Modrák, Ozturk, Peng]*.

12/2: We added *[Rodriguez-Gonzalez]*.

12/1: We added *[Capsoni]*.

11/30: We added *[Abdulrahman]*.

11/28: We added ***[Lambermont]***.

11/27: We added ***[van Halem]***.

11/25: We added ***[Qin]***, and we added analysis restricted to mortality results.

11/24: We added ***[Boari]***.

11/23: We added ***[Revollo]***.

11/20: We added ***[Omrani]***.

11/19: We added ***[Falcone]***.

11/18: We added ***[Budhiraja]***.

11/14: We added ***[Sheshah]***.

11/13: We added ***[Núñez-Gil, Águila-Gordo]***.

11/12: We added ***[Simova, Simova (B)]***.

11/10: We added ***[Mathai]***.

11/9: We added ***[Self]***.

11/8: We added ***[Dhibar]***.

11/4: We added ***[Behera, Cadegiani]***.

11/1: We added ***[Trullàs]***.

10/31: We added ***[Frontera, Szente Fonseca, Tehrani]***.

10/30: We added ***[Berenguer, Faíco-Filho]***.

10/28: We added ***[Arleo, Choi]***.

10/26: We added ***[Coll, Goenka, Synolaki]***.

10/23: We added ***[Komissarov, Lano]***. The second version of the preprint for ***[Komissarov]*** includes a comparison with the control group (not reported in the first version). We updated ***[Lyngbakken]*** to use the mortality result in the recent journal version of the paper (not reported in the preprint).

10/22: We added ***[Anglemyer, Ñamendys-Silva]***. We updated the discussion of ***[Axfors]*** for the second version of this study. We added a table summarizing RCT results.

10/21: We added studies ***[Dubee, Martinez-Lopez, Solh]***. We received a report that the United States National Institutes of Health is recommending against HCQ for hospitalized and non-hospitalized patients as of October 9, and we added a reference.

10/20/2020: Initial revision.

Appendix 1. Methods and Study Results

We performed ongoing searches of PubMed, medRxiv, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Collabovid, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19hcq.com, which regularly receives submissions of both positive and negative studies upon publication. Search terms were hydroxychloroquine or chloroquine and COVID-19 or SARS-CoV-2, or simply hydroxychloroquine or chloroquine. Automated searches are performed every hour with notifications of new matches. All studies regarding the use of HCQ or CQ for COVID-19 that report a result compared to a control group are included in the main analysis. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in calculations for that study. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days are used. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms were not used (the next most serious outcome is used — no studies were excluded). For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcome is considered more important than PCR testing status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available (after most or all patients have recovered there is no room for an effective treatment to do better). When results provide an odds ratio, we computed the relative risk when possible, or converted to a relative risk according to ***[Zhang]***. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported including propensity score matching (PSM), the PSM results are used. When needed, conversion between reported *p*-values and confidence intervals followed ***[Altman, Altman (B)]***, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 ***[Sweeting]***. If a study separates HCQ and HCQ+AZ, we use the combined results were possible, or the results for the larger group. Results are all expressed with RR < 1.0 suggesting effectiveness. Most results are the relative risk of something negative. If a study reports relative times, the results are expressed as the ratio of the time for the HCQ group versus the time for the control group. If a study reports the rate of reduction of viral load, the results are based on the percentage change in the rate. Calculations are done in Python (3.9.9) with scipy (1.7.3), pythonmeta (1.26), numpy (1.21.4), statsmodels (0.14.0), and plotly (5.4.0).

The forest plots are computed using PythonMeta ***[Deng]*** with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case).

We received no funding, this research is done in our spare time. We have no affiliations with any pharmaceutical companies or political parties.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment, and treatment started within 5 days after the onset of symptoms, although a shorter time may be preferable. Antivirals are typically only considered effective when used within a

shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective *[McLean, Treanor]*.

A summary of study results is below. Please submit updates and corrections at https://hcqmeta.com/.

Early treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. Only the first (most serious) outcome is used in pooled analysis, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

[Agusti], 12/9/2020, prospective, Spain, Europe, peer-reviewed, median age 37.0, 13 authors, dosage 400mg bid day 1, 200mg bid days 2-5.	risk of progression, 68.4% lower, RR 0.32, *p* = 0.21, treatment 2 of 87 (2.3%), control 4 of 55 (7.3%), NNT 20, pneumonia.
[Amaravadi], 2/26/2021, Double Blind Randomized Controlled Trial, USA, North America, preprint, 20 authors, dosage 400mg bid days 1-14.	risk of not reaching lowest symptom score at day 7 mid-recovery, 60.0% lower, RR 0.40, *p* = 0.13, treatment 3 of 15 (20.0%), control 6 of 12 (50.0%), NNT 3.3.
	relative time to first occurrence of lowest symptom score, 42.9% lower, relative time 0.57, *p* = 0.21, treatment 15, control 12.
	relative time to release from quarantine, 27.3% lower, relative time 0.73, *p* = 0.28, treatment 16, control 13.
[Ashraf], 4/24/2020, retrospective, database analysis, Iran, Middle East, preprint, median age 58.0, 16 authors, dosage 200mg bid daily, 400mg qd was used when combined with Lopinavir-Ritonavir.	risk of death, 67.5% lower, RR 0.32, *p* = 0.15, treatment 10 of 77 (13.0%), control 2 of 5 (40.0%), NNT 3.7.
[Bernabeu-Wittel], 8/1/2020, retrospective, Spain, Europe, peer-reviewed, 13 authors, dosage 400mg bid day 1, 200mg bid days 2-7.	risk of death, 59.0% lower, RR 0.41, *p* = 0.03, treatment 189, control 83.
[Cadegiani], 11/4/2020, prospective, Brazil, South America, peer-reviewed, 4 authors, dosage 400mg days 1-5.	risk of death, 81.2% lower, RR 0.19, *p* = 0.21, treatment 0 of 159 (0.0%), control 2 of 137 (1.5%), NNT 68, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), control group 1.

	risk of mechanical ventilation, 95.1% lower, RR 0.05, $p < 0.001$, treatment 0 of 159 (0.0%), control 9 of 137 (6.6%), NNT 15, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), control group 1.
	risk of hospitalization, 98.3% lower, RR 0.02, $p < 0.001$, treatment 0 of 159 (0.0%), control 27 of 137 (19.7%), NNT 5.1, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), control group 1.
[Chechter], 11/5/2021, prospective, Brazil, South America, preprint, 13 authors, dosage 800mg day 1, 400mg days 2-5, excluded in exclusion analyses: unadjusted results with no group details.	**risk of hospitalization, 94.7% lower, RR 0.05, $p = 0.004$**, treatment 0 of 60 (0.0%), control 3 of 12 (25.0%), NNT 4.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
[Chen], 6/22/2020, Randomized Controlled Trial, China, Asia, preprint, 19 authors, dosage 200mg bid days 1-10.	**median time to PCR-, 72.0% lower, relative time 0.28, $p = 0.01$**, treatment 18, control 12.
[Derwand], 7/3/2020, retrospective, USA, North America, peer-reviewed, 3 authors, dosage 200mg bid days 1-5, this trial uses multiple treatments in the treatment arm (combined with zinc and azithromycin) - results of individual treatments may vary.	**risk of death, 79.4% lower, RR 0.21, $p = 0.12$**, treatment 1 of 141 (0.7%), control 13 of 377 (3.4%), NNT 37, odds ratio converted to relative risk.
	risk of hospitalization, 81.6% lower, RR 0.18, $p < 0.001$, treatment 4 of 141 (2.8%), control 58 of 377 (15.4%), NNT 8.0, odds ratio converted to relative risk.
[Esper], 4/15/2020, prospective, Brazil, South America, preprint, 15 authors, dosage 800mg day 1, 400mg days 2-7.	**risk of hospitalization, 64.0% lower, RR 0.36, $p = 0.02$**, treatment 8 of 412 (1.9%), control 12 of 224 (5.4%), NNT 29.
[Gautret], 3/17/2020, prospective, France, Europe, peer-reviewed, 18 authors, dosage 200mg tid days 1-10, excluded in exclusion analyses: excessive unadjusted differences between groups, results only for PCR status which may be significantly different to symptoms.	**risk of no virological cure at day 6, 66.0% lower, RR 0.34, $p = 0.001$**, treatment 6 of 20 (30.0%), control 14 of 16 (87.5%), NNT 1.7.
[Guisado-Vasco], 10/15/2020,	**risk of death, 66.9% lower, RR 0.33, $p = 0.19$**,

retrospective, Spain, Europe, peer-reviewed, median age 69.0, 25 authors, early treatment subset, dosage not specified.	treatment 2 of 65 (3.1%), control 139 of 542 (25.6%), NNT 4.4, adjusted per study, odds ratio converted to relative risk, multivariate.
[Guérin], 5/31/2020, retrospective, France, Europe, peer-reviewed, 8 authors, dosage 600mg days 1-10, 7-10 days.	**risk of death, 61.4% lower, RR 0.39, p = 1.00**, treatment 0 of 20 (0.0%), control 1 of 34 (2.9%), NNT 34, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	recovery time, 65.0% lower, relative time 0.35, p < 0.001, treatment 20, control 34.
[Heras], 9/2/2020, retrospective, Andorra, Europe, peer-reviewed, median age 85.0, 13 authors, dosage not specified.	**risk of death, 95.6% lower, RR 0.04, p = 0.004**, treatment 8 of 70 (11.4%), control 16 of 30 (53.3%), NNT 2.4, adjusted per study.
[Hong], 7/16/2020, retrospective, South Korea, Asia, peer-reviewed, 7 authors, dosage not specified.	**risk of prolonged viral shedding, early vs. late HCQ, 64.9% lower, RR 0.35, p = 0.001**, treatment 42, control 48, odds ratio converted to relative risk.
[Huang (B)], 5/28/2020, prospective, China, Asia, peer-reviewed, 36 authors, early treatment subset, dosage chloroquine 500mg days 1-10, two groups, 500mg qd and 500mg bid.	**time to viral-, 59.1% lower, relative time 0.41, p < 0.001**, treatment 32, control 37.
[Huang (C)], 4/1/2020, Randomized Controlled Trial, China, Asia, peer-reviewed, 18 authors, dosage chloroquine 500mg bid days 1-10.	**risk of no recovery at day 14, 91.7% lower, RR 0.08, p = 0.02**, treatment 0 of 10 (0.0%), control 6 of 12 (50.0%), NNT 2.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no improvement in pneumonia at day 14, 83.0% lower, RR 0.17, p = 0.22, treatment 10, control 12.
[Ip], 8/25/2020, retrospective, database analysis, USA, North America, peer-reviewed, 25 authors, dosage not specified.	**risk of death, 54.5% lower, RR 0.45, p = 0.43**, treatment 2 of 97 (2.1%), control 44 of 970 (4.5%), NNT 40.
	risk of ICU admission, 28.6% lower, RR 0.71, p = 0.79, treatment 3 of 97 (3.1%), control 42 of 970 (4.3%), NNT 81.
	risk of hospitalization, 37.3% lower, RR 0.63, p =

	0.04, treatment 21 of 97 (21.6%), control 305 of 970 (31.4%), NNT 10, adjusted per study, odds ratio converted to relative risk.
[Kirenga], 9/9/2020, prospective, Uganda, Africa, peer-reviewed, 29 authors, dosage not specified.	**median time to recovery, 25.6% lower, relative time 0.74, $p = 0.20$**, treatment 29, control 27.
[Ly], 8/21/2020, retrospective, France, Europe, peer-reviewed, mean age 83.0, 21 authors, dosage 200mg tid days 1-10.	**risk of death, 55.6% lower, RR 0.44, $p = 0.02$**, treatment 18 of 116 (15.5%), control 29 of 110 (26.4%), NNT 9.2, adjusted per study, odds ratio converted to relative risk.
[Million], 5/27/2021, retrospective, France, Europe, peer-reviewed, 28 authors, dosage 200mg tid days 1-10.	**risk of death, 83.0% lower, RR 0.17, $p < 0.001$**, treatment 5 of 8,315 (0.1%), control 11 of 2,114 (0.5%), NNT 217, adjusted per study.
	risk of ICU admission, 44.0% lower, RR 0.56, $p = 0.18$, treatment 17 of 8,315 (0.2%), control 7 of 2,114 (0.3%), NNT 789, adjusted per study.
	risk of hospitalization, 4.0% lower, RR 0.96, $p = 0.77$, treatment 214 of 8,315 (2.6%), control 64 of 2,114 (3.0%), NNT 220, adjusted per study.
[Mitjà], 7/16/2020, Randomized Controlled Trial, Spain, Europe, peer-reviewed, 45 authors, dosage 800mg day 1, 400mg days 2-7.	**risk of hospitalization, 16.0% lower, RR 0.84, $p = 0.64$**, treatment 8 of 136 (5.9%), control 11 of 157 (7.0%), NNT 89.
	risk of no recovery, 34.0% lower, RR 0.66, $p = 0.38$, treatment 8 of 136 (5.9%), control 14 of 157 (8.9%), NNT 33.
[Mokhtari], 4/6/2021, retrospective, Iran, Middle East, peer-reviewed, 11 authors, dosage 400mg bid day 1, 200mg bid days 2-5.	**risk of death, 69.7% lower, RR 0.30, $p < 0.001$**, treatment 27 of 7,295 (0.4%), control 287 of 21,464 (1.3%), NNT 103, adjusted per study, odds ratio converted to relative risk.
	risk of hospitalization, 35.3% lower, RR 0.65, $p < 0.001$, treatment 523 of 7,295 (7.2%), control 2,382 of 21,464 (11.1%), NNT 25, adjusted per study, odds ratio converted to relative risk.
[Omrani], 11/20/2020, Randomized Controlled Trial, Qatar, Middle East, peer-reviewed, 19 authors, dosage 600mg days 1-6.	**risk of hospitalization, 12.5% lower, RR 0.88, $p = 1.00$**, treatment 7 of 304 (2.3%), control 4 of 152 (2.6%), NNT 304, HCQ+AZ or HCQ vs. control.

	risk of symptomatic at day 21, 25.8% lower, RR 0.74, *p* = 0.58, treatment 9 of 293 (3.1%), control 6 of 145 (4.1%), NNT 94, HCQ+AZ or HCQ vs. control.
	risk of Ct<=40 at day 14, 10.3% higher, RR 1.10, *p* = 0.13, treatment 223 of 295 (75.6%), control 98 of 143 (68.5%), HCQ+AZ or HCQ vs. control.
[Rodrigues], 8/25/2021, Double Blind Randomized Controlled Trial, Brazil, South America, peer-reviewed, 8 authors, dosage 400mg bid days 1-7.	**risk of hospitalization, 200.0% higher, RR 3.00, *p* = 1.00**, treatment 1 of 42 (2.4%), control 0 of 42 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of no virological cure, 14.4% lower, RR 0.86, *p* = 0.15, treatment 29 of 36 (80.6%), control 32 of 34 (94.1%), NNT 7.4, PP, day 3.
	risk of no virological cure, 13.1% lower, RR 0.87, *p* = 0.45, treatment 23 of 36 (63.9%), control 25 of 34 (73.5%), NNT 10, PP, day 6.
	risk of no virological cure, 23.3% lower, RR 0.77, *p* = 0.47, treatment 13 of 36 (36.1%), control 16 of 34 (47.1%), NNT 9.1, PP, day 9.
	risk of no virological cure, 3.1% lower, RR 0.97, *p* = 1.00, treatment 31 of 42 (73.8%), control 32 of 42 (76.2%), NNT 42, ITT, day 3.
	risk of no virological cure, no change, RR 1.00, *p* = 1.00, treatment 25 of 42 (59.5%), control 25 of 42 (59.5%), ITT, day 6.
	risk of no virological cure, 6.2% lower, RR 0.94, *p* = 1.00, treatment 15 of 42 (35.7%), control 16 of 42 (38.1%), NNT 42, ITT, day 9.
	time to viral-, 8.8% lower, relative time 0.91, *p* = 0.26, treatment 36, control 34, PP.
	time to viral-, 1.4% lower, relative time 0.99, *p* = 0.85, treatment 42, control 42, ITT.
[Roy], 3/12/2021, retrospective, database analysis, India, South Asia, preprint, 5 authors, dosage not specified, excluded	**relative time to clinical response of wellbeing, 2.4% lower, relative time 0.98, *p* = 0.96**, treatment 14, control 15.

in exclusion analyses: no serious outcomes reported and fast recovery in treatment and control groups, there is little room for a treatment to improve results.	
[Sawanpanyalert], 9/9/2021, retrospective, Thailand, South Asia, peer-reviewed, 11 authors, dosage varies, this trial uses multiple treatments in the treatment arm (combined with lopinavir/ritonavir or darunavir/ritonavir) - results of individual treatments may vary.	risk of death, ICU, intubation, or high-flow oxygen, 42.0% lower, RR 0.58, *p* = 0.37, within 4 days of symptom onset, RR approximated with OR.
[Simova], 11/12/2020, retrospective, Bulgaria, Europe, peer-reviewed, 5 authors, dosage 200mg tid days 1-14.	risk of hospitalization, 93.8% lower, RR 0.06, *p* = 0.01, treatment 0 of 33 (0.0%), control 2 of 5 (40.0%), NNT 2.5, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of viral+ at day 14, 95.8% lower, RR 0.04, *p* = 0.001, treatment 0 of 33 (0.0%), control 3 of 5 (60.0%), NNT 1.7, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
[Skipper], 7/16/2020, Randomized Controlled Trial, USA, North America, peer-reviewed, 24 authors, dosage 800mg once, followed by 600mg in 6 to 8 hours, then 600mg daily for 4 more days.	risk of death/hospitalization, 36.7% lower, RR 0.63, *p* = 0.58, treatment 5 of 231 (2.2%), control 8 of 234 (3.4%), NNT 80, COVID-19 adjudicated hospitalization/death.
	risk of hospitalization, 49.4% lower, RR 0.51, *p* = 0.38, treatment 4 of 231 (1.7%), control 8 of 234 (3.4%), NNT 59, COVID-19 adjudicated hospitalization.
	risk of death/hospitalization, 49.4% lower, RR 0.51, *p* = 0.29, treatment 5 of 231 (2.2%), control 10 of 234 (4.3%), NNT 47, all hospitalization/death.
	risk of hospitalization, 59.5% lower, RR 0.41, *p* = 0.17, treatment 4 of 231 (1.7%), control 10 of 234 (4.3%), NNT 39, all hospitalizations.
	risk of no recovery at day 14, 20.0% lower, RR 0.80, *p* = 0.21, treatment 231, control 234.

[Sobngwi], 7/29/2021, Randomized Controlled Trial, Cameroon, Africa, preprint, 16 authors, dosage 400mg days 1-5, this trial compares with another treatment - results may be better when compared to placebo.	**risk of no recovery, 51.6% lower, RR 0.48, p = 0.44**, treatment 2 of 95 (2.1%), control 4 of 92 (4.3%), NNT 45, day 10.
	risk of no recovery, 3.2% lower, RR 0.97, p = 1.00, treatment 18 of 95 (18.9%), control 18 of 92 (19.6%), NNT 162, day 3.
	risk of no virological cure, 3.2% lower, RR 0.97, p = 0.88, treatment 32 of 95 (33.7%), control 32 of 92 (34.8%), NNT 91, day 10.
[Su], 12/23/2020, retrospective, China, Asia, peer-reviewed, 9 authors, dosage 400mg days 1-10, 400mg daily for 10-14 days.	**risk of progression, 84.9% lower, RR 0.15, p = 0.006**, treatment 261, control 355, adjusted per study, binary logistic regression.
	improvement time, 24.0% lower, relative time 0.76, p = 0.02, treatment 261, control 355, adjusted per study, Cox proportional hazards regression.
[Sulaiman], 9/13/2020, prospective, Saudi Arabia, Middle East, preprint, 22 authors, dosage 400mg bid day 1, 200mg bid days 2-5.	**risk of death, 63.7% lower, RR 0.36, p = 0.01**, treatment 7 of 1,817 (0.4%), control 54 of 3,724 (1.5%), NNT 94, adjusted per study, odds ratio converted to relative risk.
	risk of hospitalization, 38.6% lower, RR 0.61, p = 0.001, treatment 171 of 1,817 (9.4%), control 617 of 3,724 (16.6%), NNT 14, adjusted per study, odds ratio converted to relative risk.
[Szente Fonseca], 10/31/2020, retrospective, Brazil, South America, peer-reviewed, mean age 50.6, 10 authors, dosage 400mg bid day 1, 400mg qd days 2-5.	**risk of hospitalization, 64.0% lower, RR 0.36, p < 0.001**, treatment 25 of 175 (14.3%), control 89 of 542 (16.4%), NNT 47, adjusted per study, odds ratio converted to relative risk, HCQ vs. nothing.
	risk of hospitalization, 50.5% lower, RR 0.49, p = 0.006, treatment 25 of 175 (14.3%), control 89 of 542 (16.4%), NNT 47, adjusted per study, odds ratio converted to relative risk, HCQ vs. anything else.
[Yu], 8/3/2020, retrospective, China, Asia, preprint, median age 62.0, 6 authors, early treatment subset, dosage 200mg bid days 1-10.	**risk of death, 85.0% lower, RR 0.15, p = 0.02**, treatment 1 of 73 (1.4%), control 238 of 2,604 (9.1%), NNT 13, HCQ treatment started early vs. non-HCQ.

Late treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. Only the first (most serious) outcome is used in pooled analysis, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

[Abd-Elsalam], 8/14/2020, Randomized Controlled Trial, Egypt, Africa, peer-reviewed, 10 authors.	**risk of death, 20.0% higher, RR 1.20, *p* = 1.00**, treatment 6 of 97 (6.2%), control 5 of 97 (5.2%).
	risk of no recovery at day 28, 30.0% lower, RR 0.70, *p* = 0.009, treatment 45 of 97 (46.4%), control 64 of 97 (66.0%), NNT 5.1.
[Abdulrahman], 11/30/2020, retrospective, propensity score matching, Bahrain, Middle East, preprint, 9 authors.	**risk of death, 16.7% lower, RR 0.83, *p* = 1.00**, treatment 5 of 223 (2.2%), control 6 of 223 (2.7%), NNT 223, PSM.
	risk of death/intubation, 75.0% higher, RR 1.75, *p* = 0.24, treatment 12 of 223 (5.4%), control 7 of 223 (3.1%), adjusted per study, PSM.
[Ader], 10/6/2020, Randomized Controlled Trial, multiple countries, multiple regions, peer-reviewed, baseline oxygen requirements 95.4%, 58 authors, excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline.	**risk of death at day 29, 6.4% lower, RR 0.94, *p* = 1.00**, treatment 11 of 145 (7.6%), control 12 of 148 (8.1%), NNT 192.
[Aghajani], 4/29/2021, retrospective, Iran, Middle East, peer-reviewed, 7 authors.	**risk of death, 19.5% lower, RR 0.81, *p* = 0.09**, treatment 553, control 438, multivariate Cox proportional regression.
[Alamdari], 9/9/2020, retrospective, Iran, Middle East, peer-reviewed, 14 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	**risk of death, 55.0% lower, RR 0.45, *p* = 0.03**, treatment 54 of 427 (12.6%), control 9 of 32 (28.1%), NNT 6.5.
[Albani], 8/30/2020, retrospective, Italy, Europe, peer-reviewed, 11 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage	**risk of death, 18.4% lower, RR 0.82, *p* = 0.15**, treatment 60 of 211 (28.4%), control 172 of 605 (28.4%), adjusted per study, odds ratio converted to relative risk, HCQ vs. neither.
	risk of death, 9.0% higher, RR 1.09, *p* = 0.54, treatment 60 of 211 (28.4%), control 172 of 605

over the early stages of the pandemic when overall treatment protocols improved dramatically.	(28.4%), adjusted per study, odds ratio converted to relative risk, HCQ+AZ vs. neither.
	risk of ICU admission, 9.2% higher, RR 1.09, p = 0.70, treatment 73 of 211 (34.6%), control 46 of 605 (7.6%), adjusted per study, odds ratio converted to relative risk, HCQ vs. neither.
	risk of ICU admission, 71.3% higher, RR 1.71, p < 0.001, treatment 73 of 211 (34.6%), control 46 of 605 (7.6%), adjusted per study, odds ratio converted to relative risk, HCQ+AZ vs. neither.
[Alberici], 5/10/2020, retrospective, Italy, Europe, peer-reviewed, 31 authors.	**risk of death, 42.9% lower, RR 0.57, p = 0.12**, treatment 17 of 72 (23.6%), control 9 of 22 (40.9%), NNT 5.8, odds ratio converted to relative risk.
[Alghamdi], 8/4/2021, retrospective, Saudi Arabia, Middle East, peer-reviewed, 1 author, excluded in exclusion analyses: unadjusted results with no group details, very late stage, ICU patients.	**risk of death, 39.2% higher, RR 1.39, p = 0.52**, treatment 29 of 128 (22.7%), control 7 of 43 (16.3%).
[Alghamdi (B)], 3/31/2021, retrospective, Saudi Arabia, Middle East, peer-reviewed, 10 authors, excluded in exclusion analyses: confounding by indication is likely and adjustments do not consider COVID-19 severity.	**risk of death, 6.9% higher, RR 1.07, p = 0.88**, treatment 44 of 568 (7.7%), control 15 of 207 (7.2%).
[Alhamlan], 7/16/2021, retrospective, database analysis, Saudi Arabia, Middle East, preprint, 10 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	**risk of death, 52.0% higher, RR 1.52, p = 0.57**.
[Almazrou], 10/1/2020, retrospective, Saudi Arabia, Middle East, peer-reviewed, 5 authors.	**risk of mechanical ventilation, 65.0% lower, RR 0.35, p = 0.16**, treatment 3 of 95 (3.2%), control 6 of 66 (9.1%), NNT 17.
	risk of ICU admission, 21.0% lower, RR 0.79, p =

	0.78, treatment 8 of 95 (8.4%), control 7 of 66 (10.6%), NNT 46.
[Alotaibi], 9/14/2021, retrospective, Saudi Arabia, Middle East, peer-reviewed, 11 authors, this trial compares with another treatment - results may be better when compared to placebo.	**risk of death, 133.5% higher, RR 2.33, *p* = 0.05**, treatment 193, control 244, multivariate.
[Alqassieh], 12/10/2020, prospective, Jordan, Middle East, preprint, 10 authors.	**hospitalization time, 18.2% lower, relative time 0.82, *p* = 0.11**, treatment 63, control 68.
[An], 7/7/2020, retrospective, South Korea, Asia, preprint, 12 authors.	**time to viral clearance, 3.0% lower, RR 0.97, *p* = 0.92**, treatment 31, control 195.
[Annie], 10/12/2020, retrospective, database analysis, USA, North America, peer-reviewed, 5 authors, excluded in exclusion analyses: confounding by indication is likely and adjustments do not consider COVID-19 severity.	**risk of death, 4.3% lower, RR 0.96, *p* = 0.83**, treatment 48 of 367 (13.1%), control 50 of 367 (13.6%), NNT 183, odds ratio converted to relative risk.
	risk of death, 20.5% higher, RR 1.21, *p* = 0.46, treatment 29 of 199 (14.6%), control 24 of 199 (12.1%), odds ratio converted to relative risk.
[Aparisi], 10/8/2020, prospective, Spain, Europe, preprint, 18 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 63.0% lower, RR 0.37, *p* = 0.008**, treatment 122 of 605 (20.2%), control 27 of 49 (55.1%), NNT 2.9.
[Arshad], 7/1/2020, retrospective, USA, North America, peer-reviewed, 12 authors.	**risk of death, 51.3% lower, RR 0.49, *p* = 0.009**, treatment 162 of 1,202 (13.5%), control 108 of 409 (26.4%), NNT 7.7.
[Ashinyo], 9/15/2020, retrospective, Ghana, Africa, peer-reviewed, 16 authors.	**hospitalization time, 33.0% lower, relative time 0.67, *p* = 0.03**, treatment 61, control 61.
[Auld], 4/26/2020, retrospective, USA, North America, peer-reviewed, 14 authors.	**risk of death, 2.8% higher, RR 1.03, *p* = 1.00**, treatment 33 of 114 (28.9%), control 29 of 103 (28.2%).
[Awad], 2/18/2021, retrospective, USA, North America, peer-reviewed, 4 authors, excluded in exclusion analyses: substantial time varying confounding likely due to declining usage over the early stages of the pandemic when	**risk of death, 19.1% higher, RR 1.19, *p* = 0.60**, treatment 56 of 188 (29.8%), control 37 of 148 (25.0%).
	risk of mechanical ventilation, 460.7% higher, RR 5.61, *p* < 0.001, treatment 64 of 188 (34.0%), control 9 of 148 (6.1%), adjusted per study, odds

overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.	ratio converted to relative risk.
	risk of ICU admission, 463.4% higher, RR 5.63, $p < 0.001$, treatment 67 of 188 (35.6%), control 9 of 148 (6.1%), adjusted per study, odds ratio converted to relative risk.
[Ayerbe], 9/30/2020, retrospective, database analysis, Spain, Europe, peer-reviewed, 3 authors.	**risk of death, 52.2% lower, RR 0.48, $p < 0.001$**, treatment 237 of 1,857 (12.8%), control 49 of 162 (30.2%), NNT 5.7, adjusted per study, odds ratio converted to relative risk.
[Babalola], 10/1/2021, Single Blind Randomized Controlled Trial, Nigeria, Africa, preprint, 6 authors, this trial uses multiple treatments in the treatment arm (combined with AZ) - results of individual treatments may vary.	**risk of no hospital discharge, 54.5% higher, RR 1.55, $p = 0.20$**, treatment 17 of 30 (56.7%), control 11 of 30 (36.7%), day 7.
	risk of no virological cure, 9.5% lower, RR 0.90, $p = 0.78$, treatment 19 of 30 (63.3%), control 21 of 30 (70.0%), NNT 15, day 5 mid-recovery.
[Barbosa], 4/12/2020, retrospective, USA, North America, preprint, 5 authors, excluded in exclusion analyses: excessive unadjusted differences between groups.	**risk of death, 147.0% higher, RR 2.47, $p = 0.58$**, treatment 2 of 17 (11.8%), control 1 of 21 (4.8%).
[Barra], 7/31/2021, retrospective, Argentina, South America, preprint, 12 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 10.8% lower, RR 0.89, $p = 1.00$**, treatment 2 of 18 (11.1%), control 81 of 650 (12.5%), NNT 74, unadjusted.
[Barrat-Due], 7/13/2021, Double Blind Randomized Controlled Trial, Norway, Europe, peer-reviewed, 41 authors.	**risk of death, 120.0% higher, RR 2.20, $p = 0.35$**, treatment 4 of 45 (8.9%), control 2 of 48 (4.2%), adjusted per study.
[Barry], 3/23/2021, retrospective, Saudi Arabia, Middle East, peer-reviewed, 14 authors.	**risk of death, 98.9% lower, RR 0.01, $p = 0.60$**, treatment 0 of 6 (0.0%), control 91 of 599 (15.2%), NNT 6.6, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
[Berenguer], 8/3/2020, retrospective, Spain, Europe, peer-reviewed, 8 authors.	**risk of death, 18.2% lower, RR 0.82, $p < 0.001$**, treatment 681 of 2,618 (26.0%), control 438 of 1,377 (31.8%), NNT 17.
[Bernaola], 7/21/2020, retrospective, Spain, Europe, preprint, 7 authors.	**risk of death, 17.0% lower, RR 0.83, $p < 0.001$**, treatment 236 of 1,498 (15.8%), control 28 of 147

	(19.0%), NNT 30.
[Bielza], 12/11/2020, retrospective, Spain, Europe, peer-reviewed, median age 87.0, 24 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 21.5% lower, RR 0.78, p = 0.09**, treatment 33 of 91 (36.3%), control 249 of 539 (46.2%), NNT 10.
[Boari], 11/17/2020, retrospective, Italy, Europe, peer-reviewed, 20 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 54.5% lower, RR 0.45, p < 0.001**, treatment 41 of 202 (20.3%), control 25 of 56 (44.6%), NNT 4.1.
[Bosaeed], 4/30/2021, Randomized Controlled Trial, Saudi Arabia, Middle East, peer-reviewed, 30 authors, excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline.	**risk of death, 3.7% lower, RR 0.96, p = 0.91**, treatment 14 of 125 (11.2%), control 15 of 129 (11.6%), NNT 234, 90 days.
	risk of death, 28.6% lower, RR 0.71, p = 0.45, treatment 9 of 125 (7.2%), control 13 of 129 (10.1%), NNT 35, 28 days.
	risk of death, 65.1% higher, RR 1.65, p = 0.68, treatment 8 of 125 (6.4%), control 5 of 129 (3.9%), 14 days.
	risk of mechanical ventilation, 8.4% higher, RR 1.08, p = 0.78, treatment 21 of 125 (16.8%), control 20 of 129 (15.5%).
	risk of ICU admission, 31.0% higher, RR 1.31, p = 0.24, treatment 33 of 125 (26.4%), control 26 of 129 (20.2%).
	recovery time, 28.6% higher, relative time 1.29, p = 0.29, treatment 125, control 129.
	hospitalization time, 12.5% higher, relative time 1.12, p = 0.42, treatment 125, control 129.
	risk of no virological cure, 2.6% lower, RR 0.97, p = 0.75, treatment 100 of 125 (80.0%), control 106 of 129 (82.2%), NNT 46.
[Bousquet], 6/23/2020, prospective, France, Europe, peer-reviewed, 10 authors.	**risk of death, 42.8% lower, RR 0.57, p = 0.15**, treatment 5 of 27 (18.5%), control 23 of 81 (28.4%), NNT 10, adjusted per study, odds ratio converted to relative risk.

[Budhiraja], 11/18/2020, retrospective, India, South Asia, preprint, 12 authors, excluded in exclusion analyses: excessive unadjusted differences between groups.	**risk of death, 65.4% lower, RR 0.35, $p < 0.001$**, treatment 69 of 834 (8.3%), control 34 of 142 (23.9%), NNT 6.4.
[Burdick], 11/26/2020, prospective, USA, North America, peer-reviewed, 14 authors.	**risk of death, 59.0% higher, RR 1.59, $p = 0.12$**, treatment 142, control 148, adjusted per study, all patients.
	risk of death, 71.0% lower, RR 0.29, $p = 0.01$, treatment 26, control 17, adjusted per study, subgroup of patients where treatment is predicted to be beneficial.
[Byakika-Kibwika], 6/4/2021, Randomized Controlled Trial, Uganda, Africa, preprint, 17 authors.	**recovery time, no change, relative time 1.00, $p = 0.91$**, treatment 36, control 29.
	relative improvement in Ct value, 29.3% better, RR 0.71, $p = 0.47$, treatment 15, control 15.
	risk of no virological cure, 2.6% higher, RR 1.03, $p = 1.00$, treatment 35 of 55 (63.6%), control 31 of 50 (62.0%), day 6.
	risk of no virological cure, 6.7% higher, RR 1.07, $p = 0.85$, treatment 27 of 55 (49.1%), control 23 of 50 (46.0%), day 10.
[Calderón], 11/23/2021, retrospective, Mexico, North America, peer-reviewed, 7 authors, dosage 200mg bid days 1-7.	**risk of death, 214.8% higher, RR 3.15, $p = 0.38$**, treatment 5 of 27 (18.5%), control 1 of 17 (5.9%).
	risk of mechanical ventilation, 651.9% higher, RR 7.52, $p = 0.15$, treatment 4 of 27 (14.8%), control 0 of 17 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of ICU admission, 145.5% higher, RR 2.45, $p < 0.001$, treatment 16 of 27 (59.3%), control 0 of 17 (0.0%), adjusted per study.
	hospitalization time, 107.4% higher, relative time 2.07, $p = 0.006$, treatment 27, control 17.
[Cangiano], 12/22/2020, retrospective, Italy, Europe, peer-reviewed, 14 authors.	**risk of death, 73.4% lower, RR 0.27, $p = 0.03$**, treatment 5 of 33 (15.2%), control 37 of 65 (56.9%), NNT 2.4.

[Capsoni], 12/1/2020, retrospective, Italy, Europe, preprint, 13 authors.	**risk of mechanical ventilation, 40.0% lower, RR 0.60, p = 0.30**, treatment 12 of 40 (30.0%), control 6 of 12 (50.0%), NNT 5.0.
[Catteau], 8/24/2020, retrospective, database analysis, Belgium, Europe, peer-reviewed, 11 authors.	**risk of death, 32.0% lower, RR 0.68, p < 0.001**, treatment 804 of 4,542 (17.7%), control 957 of 3,533 (27.1%), NNT 11.
[Cavalcanti], 7/23/2020, Randomized Controlled Trial, Brazil, South America, peer-reviewed, baseline oxygen requirements 41.8%, 14 authors.	**risk of death, 16.0% lower, RR 0.84, p = 0.77**, treatment 8 of 331 (2.4%), control 5 of 173 (2.9%), NNT 211, HCQ+HCQ/AZ.
	risk of hospitalization, 28.0% higher, RR 1.28, p = 0.30, treatment 331, control 173, HCQ+HCQ/AZ.
[Chari], 12/24/2020, retrospective, multiple countries, multiple regions, peer-reviewed, median age 69.0, 25 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 33.1% lower, RR 0.67, p = 0.17**, treatment 8 of 29 (27.6%), control 195 of 473 (41.2%), NNT 7.3.
[Chen (B)], 7/10/2020, Randomized Controlled Trial, Taiwan, Asia, peer-reviewed, 19 authors.	**risk of no virological cure, 24.0% lower, RR 0.76, p = 0.71**, treatment 4 of 21 (19.0%), control 3 of 12 (25.0%), NNT 17, day 14.
	median time to PCR-, 50.0% lower, relative time 0.50, p = 0.40, treatment 21, control 12.
[Chen (C)], 7/10/2020, retrospective, Taiwan, Asia, peer-reviewed, 19 authors.	**risk of no virological cure, 29.0% higher, RR 1.29, p = 0.70**, treatment 16 of 28 (57.1%), control 4 of 9 (44.4%), day 14.
[Chen (D)], 3/31/2020, Randomized Controlled Trial, China, Asia, preprint, 9 authors.	**risk of no improvement in pneumonia at day 6, 57.0% lower, RR 0.43, p = 0.04**, treatment 6 of 31 (19.4%), control 14 of 31 (45.2%), NNT 3.9.
[Chen (E)], 3/6/2020, Randomized Controlled Trial, China, Asia, peer-reviewed, 14 authors.	**risk of radiological progression, 29.0% lower, RR 0.71, p = 0.57**, treatment 5 of 15 (33.3%), control 7 of 15 (46.7%), NNT 7.5.
	risk of viral+ at day 7, 100% higher, RR 2.00, p = 1.00, treatment 2 of 15 (13.3%), control 1 of 15 (6.7%).
[Choi], 10/27/2020, retrospective, database analysis, South Korea, Asia,	**median time to PCR-, 22.0% higher, relative time 1.22, p < 0.001**, treatment 701, control 701.

peer-reviewed, 8 authors, excluded in exclusion analyses: excessive unadjusted differences between groups.	
[Colll], 10/23/2020, retrospective, Spain, Europe, peer-reviewed, median age 61.0, 29 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 45.6% lower, RR 0.54, $p < 0.001$**, treatment 55 of 307 (17.9%), control 108 of 328 (32.9%), NNT 6.7.
[Cravedi], 7/10/2020, retrospective, USA, North America, peer-reviewed, mean age 60.0, 25 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	**risk of death, 53.0% higher, RR 1.53, $p = 0.17$**, treatment 36 of 101 (35.6%), control 10 of 43 (23.3%).
[D'Arminio Monforte], 7/29/2020, retrospective, Italy, Europe, preprint, 5 authors.	**risk of death, 34.0% lower, RR 0.66, $p = 0.12$**, treatment 53 of 197 (26.9%), control 47 of 92 (51.1%), NNT 4.1, adjusted per study.
[Davido], 8/2/2020, retrospective, France, Europe, peer-reviewed, 14 authors.	**risk of intubation/hospitalization, 55.0% lower, RR 0.45, $p = 0.04$**, treatment 12 of 80 (15.0%), control 13 of 40 (32.5%), NNT 5.7.
[De Luna], 12/14/2020, retrospective, Dominican Republic, Caribbean, preprint, 10 authors, excluded in exclusion analyses: unadjusted results with no group details, substantial unadjusted confounding by indication likely.	**risk of death, 104.5% higher, RR 2.05, $p = 0.69$**, treatment 15 of 132 (11.4%), control 1 of 18 (5.6%).
[De Rosa], 5/1/2021, retrospective, Italy, Europe, peer-reviewed, 20 authors.	**risk of death, 35.0% lower, RR 0.65, $p = 0.02$**, treatment 118 of 731 (16.1%), control 80 of 280 (28.6%), NNT 8.0, adjusted per study, odds ratio converted to relative risk, multivariate logistic regression, patients alive at day 7.
[Di Castelnuovo], 1/29/2021, retrospective, Italy, Europe, peer-reviewed, 112 authors.	**risk of death, 40.0% lower, RR 0.60, $p < 0.001$**, treatment 3,270, control 1,000, odds ratio converted to relative risk, multivariate Cox proportional hazards model 4, control prevalence approximated with overall prevalence.
[Di Castelnuovo (B)], 8/25/2020, retrospective, Italy, Europe, peer-reviewed, 110 authors.	**risk of death, 30.0% lower, RR 0.70, $p < 0.001$**, treatment 386 of 2,634 (14.7%), control 90 of 817 (11.0%), adjusted per study.

[Dubee], 10/21/2020, Randomized Controlled Trial, France, Europe, peer-reviewed, median age 77.0, 18 authors.	**risk of death at day 28, 46.0% lower, RR 0.54, *p* = 0.21**, treatment 6 of 124 (4.8%), control 11 of 123 (8.9%), NNT 24.
	risk of combined intubation/death at day 28, 26.0% lower, RR 0.74, *p* = 0.48, treatment 9 of 124 (7.3%), control 12 of 123 (9.8%), NNT 40.
[Dubernet], 8/20/2020, retrospective, France, Europe, peer-reviewed, median age 66.0, 20 authors.	**risk of ICU admission, 87.6% lower, RR 0.12, *p* = 0.008**, treatment 1 of 17 (5.9%), control 9 of 19 (47.4%), NNT 2.4.
[Falcone], 11/19/2020, prospective, propensity score matching, Italy, Europe, peer-reviewed, 19 authors.	**risk of death, 65.0% lower, RR 0.35, *p* = 0.20**, treatment 40 of 238 (16.8%), control 30 of 77 (39.0%), NNT 4.5, adjusted per study, PSM.
	risk of death, 25.0% lower, RR 0.75, *p* = 0.36, treatment 40 of 238 (16.8%), control 30 of 77 (39.0%), NNT 4.5, adjusted per study, multivariate Cox regression.
	risk of death, 57.0% lower, RR 0.43, *p* < 0.001, treatment 40 of 238 (16.8%), control 30 of 77 (39.0%), NNT 4.5, adjusted per study, univariate Cox regression.
[Faíco-Filho], 6/21/2020, prospective, Brazil, South America, peer-reviewed, median age 58.0, 6 authors.	**Δt7-12 ΔCt improvement, 80.8% lower, relative rate 0.19, *p* = 0.40**, treatment 34, control 32.
	Δt<7 ΔCt improvement, 24.0% lower, relative rate 0.76, *p* = 0.36, treatment 34, control 32.
	Δt>12 ΔCt improvement, 15.0% higher, relative rate 1.15, *p* = 0.52, treatment 34, control 32.
[Ferreira], 11/26/2021, retrospective, Brazil, South America, peer-reviewed, 5 authors, 12 March, 2020 - 8 July, 2020, dosage not specified.	**risk of death, 151.5% higher, RR 2.51, *p* = 0.03**, treatment 17 of 111 (15.3%), control 11 of 81 (13.6%), odds ratio converted to relative risk, multivariate.
	risk of death/intubation, 45.9% higher, RR 1.46, *p* = 0.23, treatment 30 of 111 (27.0%), control 15 of 81 (18.5%).
	risk of death/intubation/ICU, 61.3% higher, RR 1.61, *p* = 0.04, treatment 42 of 111 (37.8%), control 19 of 81 (23.5%).

[Fontana], 6/22/2020, retrospective, Italy, Europe, peer-reviewed, 8 authors.	**risk of death, 50.0% lower, RR 0.50, p = 0.53**, treatment 4 of 12 (33.3%), control 2 of 3 (66.7%), NNT 3.0.
[Fried], 8/28/2020, retrospective, database analysis, USA, North America, peer-reviewed, 11 authors, excluded in exclusion analyses: excessive unadjusted differences between groups, substantial unadjusted confounding by indication likely.	**risk of death, 27.0% higher, RR 1.27, p < 0.001**, treatment 1,048 of 4,232 (24.8%), control 1,466 of 7,489 (19.6%).
[Frontera], 10/26/2020, retrospective, propensity score matching, USA, North America, preprint, median age 64.0, 14 authors, this trial uses multiple treatments in the treatment arm (combined with zinc) - results of individual treatments may vary.	**risk of death, 37.0% lower, RR 0.63, p = 0.01**, treatment 121 of 1,006 (12.0%), control 424 of 2,467 (17.2%), NNT 19, adjusted per study, PSM.
	risk of death, 24.0% lower, RR 0.76, p = 0.02, treatment 121 of 1,006 (12.0%), control 424 of 2,467 (17.2%), NNT 19, adjusted per study, regression.
[Gadhiya], 4/8/2021, retrospective, USA, North America, peer-reviewed, 4 authors, excluded in exclusion analyses: substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.	**risk of death, 4.8% higher, RR 1.05, p = 0.89**, treatment 22 of 55 (40.0%), control 33 of 216 (15.3%), adjusted per study, odds ratio converted to relative risk, multivariate logistic regression.
[Geleris], 5/7/2020, retrospective, USA, North America, peer-reviewed, 12 authors, excluded in exclusion analyses: significant issues found with adjustments.	**risk of death/intubation, 4.0% higher, RR 1.04, p = 0.76**, treatment 262 of 811 (32.3%), control 84 of 565 (14.9%), adjusted per study.
[Gerlovin], 6/24/2021, retrospective, USA, North America, peer-reviewed, 21 authors.	**risk of death, 22.0% higher, RR 1.22, p = 0.18**, treatment 90 of 429 (21.0%), control 141 of 770 (18.3%), adjusted per study, HCQ+AZ.
	risk of death, 21.0% higher, RR 1.21, p = 0.33, treatment 49 of 228 (21.5%), control 141 of 770 (18.3%), adjusted per study, HCQ.
	risk of mechanical ventilation, 55.0% higher, RR 1.55, p = 0.02, treatment 64 of 429 (14.9%), control

	69 of 770 (9.0%), adjusted per study, HCQ+AZ.
	risk of mechanical ventilation, 33.0% higher, RR 1.33, *p* = 0.25, treatment 32 of 228 (14.0%), control 69 of 770 (9.0%), adjusted per study, HCQ.
[Goldman], 5/27/2020, retrospective, multiple countries, multiple regions, peer-reviewed, 26 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 22.3% lower, RR 0.78, *p* = 0.46**, treatment 10 of 109 (9.2%), control 34 of 288 (11.8%), NNT 38.
[Gonzalez], 2/23/2021, Double Blind Randomized Controlled Trial, Mexico, North America, preprint, mean age 53.8, 13 authors.	**risk of death, 62.6% lower, RR 0.37, *p* = 0.27**, treatment 2 of 33 (6.1%), control 6 of 37 (16.2%), NNT 9.8.
	risk of respiratory deterioration or death, 25.3% lower, RR 0.75, *p* = 0.57, treatment 6 of 33 (18.2%), control 9 of 37 (24.3%), NNT 16.
	risk of no hospital discharge, 12.1% higher, RR 1.12, *p* = 1.00, treatment 3 of 33 (9.1%), control 3 of 37 (8.1%).
[Gonzalez (B)], 8/21/2020, retrospective, database analysis, Spain, Europe, preprint, 25 authors.	**risk of death, 26.6% lower, RR 0.73, *p* = 0.06**, treatment 1,246 of 8,476 (14.7%), control 341 of 1,168 (29.2%), NNT 6.9, adjusted per study, odds ratio converted to relative risk.
[Guglielmetti], 10/25/2021, retrospective, Italy, Europe, peer-reviewed, 19 authors, 21 February, 2020 - 15 May, 2020.	**risk of death, 28.0% lower, RR 0.72, *p* = 0.10**, treatment 474, control 126, multivariable Cox proportional hazards.
[Guglielmetti (B)], 12/9/2020, retrospective, Italy, Europe, peer-reviewed, 16 authors.	**risk of death, 35.0% lower, RR 0.65, *p* = 0.22**, treatment 181, control 37, adjusted per study, multivariable Cox.
[Guisado-Vasco (B)], 10/15/2020, retrospective, Spain, Europe, peer-reviewed, median age 69.0, 25 authors.	**risk of death, 20.3% lower, RR 0.80, *p* = 0.36**, treatment 127 of 558 (22.8%), control 14 of 49 (28.6%), NNT 17, adjusted per study, odds ratio converted to relative risk.
[Gupta], 7/15/2020, retrospective, USA, North America, peer-reviewed, baseline oxygen requirements 87.1%, 34 authors,	**risk of death, 6.0% higher, RR 1.06, *p* = 0.41**, treatment 631 of 1,761 (35.8%), control 153 of 454 (33.7%).

excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline.	
[Güner], 12/29/2020, retrospective, Turkey, Europe, peer-reviewed, 23 authors.	**risk of ICU admission, 77.3% lower, RR 0.23, p = 0.16**, treatment 604, control 100, IPTW multivariate analysis, HCQ vs. favipiravir.
[Heberto], 9/12/2020, prospective, Mexico, North America, peer-reviewed, 8 authors, this trial uses multiple treatments in the treatment arm (combined with AZ) - results of individual treatments may vary.	**risk of death, 53.9% lower, RR 0.46, p = 0.04**, treatment 139, control 115, odds ratio converted to relative risk.
	risk of mechanical ventilation, 65.1% lower, RR 0.35, p = 0.008, treatment 139, control 115, odds ratio converted to relative risk.
[Hernandez-Cardenas], 2/5/2021, Randomized Controlled Trial, Mexico, North America, preprint, 6 authors.	**risk of death, 12.0% lower, RR 0.88, p = 0.66**, treatment 106, control 108.
	risk of death, 57.0% lower, RR 0.43, p = 0.29, subgroup not intubated at baseline.
[Hraiech], 5/24/2020, retrospective, France, Europe, peer-reviewed, 8 authors, excluded in exclusion analyses: very late stage, ICU patients.	**risk of death, 64.7% lower, RR 0.35, p = 0.21**, treatment 2 of 17 (11.8%), control 5 of 15 (33.3%), NNT 4.6, day 38 +- 7.
	risk of death, 376.5% higher, RR 4.76, p = 0.49, treatment 2 of 17 (11.8%), control 0 of 15 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 6 from ARDS.
	risk of no virological cure, 2.9% higher, RR 1.03, p = 1.00, treatment 14 of 17 (82.4%), control 8 of 10 (80.0%), day 6 from treatment.
[Huang (D)], 5/28/2020, prospective, China, Asia, peer-reviewed, 36 authors.	**time to viral-, 67.0% lower, relative time 0.33, p < 0.001**, treatment 197, control 176.
	time to viral-, 59.1% lower, relative time 0.41, p < 0.001, treatment 32, control 37, early treatment.
[Ip (B)], 5/25/2020, retrospective, database analysis, USA, North America, peer-reviewed, 32 authors.	**risk of death, 1.0% lower, RR 0.99, p = 0.93**, treatment 432 of 1,914 (22.6%), control 115 of 598 (19.2%), adjusted per study.
[Izoulet], 4/21/2020, retrospective,	**risk of death, 85.0% lower, RR 0.15, p < 0.001**.

multiple countries, multiple regions, preprint, 1 author, dosage not specified, excluded in exclusion analyses: excessive unadjusted differences between groups.	
[Jacobs], 7/6/2021, prospective, USA, North America, peer-reviewed, 14 authors, excluded in exclusion analyses: unadjusted results with no group details, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	risk of death, 6.6% lower, RR 0.93, p = 0.74, treatment 24 of 46 (52.2%), control 86 of 154 (55.8%), NNT 27.
[Johnston], 12/9/2020, Randomized Controlled Trial, USA, North America, peer-reviewed, 30 authors, dosage 400mg bid day 1, 200mg bid days 2-10.	risk of hospitalization, 29.9% lower, RR 0.70, p = 0.73, treatment 5 of 148 (3.4%), control 4 of 83 (4.8%), NNT 69, HCQ + folic acid and HCQ + AZ vs. vitamin C + folic acid.
	risk of no recovery, 2.0% lower, RR 0.98, p = 0.95, treatment 30 of 60 (50.0%), control 34 of 72 (47.2%), adjusted per study, HCQ + folic acid vs. vitamin C + folic acid.
	risk of no recovery, 9.9% higher, RR 1.10, p = 0.70, treatment 34 of 65 (52.3%), control 34 of 72 (47.2%), adjusted per study, HCQ + AZ vs. vitamin C + folic acid.
	time to viral-, 14.3% lower, relative time 0.86, treatment 51, control 52, median time, HCQ + AZ vs. vitamin C + folic acid.
	risk of no virological cure, 38.3% lower, RR 0.62, p = 0.047, treatment 6 of 49 (12.2%), control 12 of 52 (23.1%), NNT 9.2, adjusted per study, HCQ + folic acid vs. vitamin C + folic acid.
	risk of no virological cure, 20.0% lower, RR 0.80, p = 0.49, treatment 11 of 51 (21.6%), control 12 of 52 (23.1%), NNT 66, adjusted per study, HCQ + AZ vs. vitamin C + folic acid.
[Kalligeros], 8/5/2020, retrospective, USA, North America, peer-reviewed, 13	risk of death, 67.0% higher, RR 1.67, p = 0.57, treatment 36, control 72.

authors.	
[Kamran], 8/4/2020, prospective, Pakistan, South Asia, preprint, 10 authors, excluded in exclusion analyses: excessive unadjusted differences between groups.	**risk of progression, 5.0% lower, RR 0.95, p = 1.00**, treatment 11 of 349 (3.2%), control 5 of 151 (3.3%), NNT 627.
	risk of progression, 54.8% lower, RR 0.45, p = 0.30, treatment 4 of 31 (12.9%), control 2 of 7 (28.6%), NNT 6.4, with comorbidities.
	risk of viral+ at day 14, 10.0% higher, RR 1.10, p = 0.52, treatment 349, control 151.
[Kelly], 7/22/2020, retrospective, Ireland, Europe, peer-reviewed, 14 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	**risk of death, 143.0% higher, RR 2.43, p = 0.03**, treatment 23 of 82 (28.0%), control 6 of 52 (11.5%).
[Kim], 5/18/2020, retrospective, South Korea, Asia, preprint, 11 authors.	**hospitalization time, 51.0% lower, relative time 0.49, p = 0.01**, treatment 22, control 40.
	time to viral-, 56.0% lower, relative time 0.44, p = 0.005, treatment 22, control 40.
[Kokturk], 4/28/2021, retrospective, database analysis, Turkey, Europe, peer-reviewed, 68 authors.	**risk of death, 3.8% higher, RR 1.04, p = 0.97**, treatment 62 of 1,382 (4.5%), control 5 of 118 (4.2%), adjusted per study, odds ratio converted to relative risk.
[Komissarov], 6/30/2020, retrospective, Russia, Europe, preprint, 8 authors.	**risk of viral load, 25.0% higher, RR 1.25, p = 0.45**, treatment 26, control 10.
[Krishnan], 7/20/2020, retrospective, USA, North America, peer-reviewed, 13 authors, dosage not specified, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 20.4% lower, RR 0.80, p = 0.48**, treatment 86 of 144 (59.7%), control 6 of 8 (75.0%), NNT 6.5.
[Kuderer], 5/28/2020, retrospective, USA, North America, peer-reviewed, 73 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	**risk of death, 134.2% higher, RR 2.34, p < 0.001**, treatment 45 of 181 (24.9%), control 121 of 928 (13.0%), odds ratio converted to relative risk, HCQ+AZ.
[Lagier], 6/4/2021, retrospective, France, Europe, preprint, 32 authors.	**risk of death, 32.0% lower, RR 0.68, p = 0.004**, treatment 93 of 1,270 (7.3%), control 146 of 841

	(17.4%), NNT 10.0, adjusted per study, weighted multivariate Cox proportional hazards model.
[Lagier (B)], 6/25/2020, retrospective, France, Europe, peer-reviewed, 22 authors, dosage 200mg tid days 1-10.	**risk of death, 59.0% lower, RR 0.41, p = 0.048**, treatment 35 of 3,119 (1.1%), control 58 of 618 (9.4%), NNT 12, adjusted per study.
[Lamback], 2/19/2021, retrospective, Brazil, South America, peer-reviewed, 10 authors, excluded in exclusion analyses: substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	**risk of death, 8.9% lower, RR 0.91, p = 0.83**, treatment 11 of 101 (10.9%), control 11 of 92 (12.0%), NNT 94.
	risk of ICU admission, 19.9% higher, RR 1.20, p = 0.61, treatment 25 of 101 (24.8%), control 19 of 92 (20.7%).
[Lambermont], 11/28/2020, retrospective, Belgium, Europe, peer-reviewed, 15 authors.	**risk of death, 32.3% lower, RR 0.68, p = 0.46**, treatment 97 of 225 (43.1%), control 14 of 22 (63.6%), NNT 4.9, adjusted per study.
[Lammers], 9/29/2020, prospective, Netherlands, Europe, peer-reviewed, 18 authors.	**risk of death/ICU, 32.0% lower, RR 0.68, p = 0.02**, treatment 30 of 189 (15.9%), control 101 of 498 (20.3%), NNT 23, adjusted per study.
[Lano], 10/21/2020, retrospective, France, Europe, peer-reviewed, median age 73.5, 30 authors.	**risk of death, 33.1% lower, RR 0.67, p = 0.28**, treatment 56, control 66, adjusted per study, odds ratio converted to relative risk.
	risk of death/ICU, 38.9% lower, RR 0.61, p = 0.23, treatment 17 of 56 (30.4%), control 28 of 66 (42.4%), NNT 8.3, adjusted per study, odds ratio converted to relative risk.
	risk of death/ICU, 68.7% lower, RR 0.31, p = 0.11, treatment 4 of 36 (11.1%), control 11 of 31 (35.5%), NNT 4.1, not requiring O2 on diagnosis (relatively early treatment).
[Lauriola], 9/14/2020, retrospective, Italy, Europe, peer-reviewed, mean age 71.8, 10 authors.	**risk of death, 73.5% lower, RR 0.27, p < 0.001**, treatment 102 of 297 (34.3%), control 35 of 63 (55.6%), NNT 4.7, adjusted per study.
[Lecronier], 7/11/2020, retrospective, France, Europe, peer-reviewed, baseline oxygen requirements 100.0%, 25	**risk of death, 42.0% lower, RR 0.58, p = 0.24**, treatment 9 of 38 (23.7%), control 9 of 22 (40.9%), NNT 5.8.
	risk of treatment escalation, 6.0% lower, RR 0.94, p

authors, HCQ vs. control, excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline.	= 0.73, treatment 15 of 38 (39.5%), control 9 of 22 (40.9%), NNT 70.
	risk of viral+ at day 7, 15.0% lower, RR 0.85, *p* = 0.61, treatment 19 of 26 (73.1%), control 12 of 14 (85.7%), NNT 7.9.
[Li], 1/18/2021, retrospective, China, Asia, peer-reviewed, 21 authors.	**risk of no hospital discharge, 50.0% lower, RR 0.50, *p* = 0.09**, treatment 14, control 14, RCT patients vs. matched sample of non-treated patients.
[Li (B)], 1/12/2021, retrospective, database analysis, China, Asia, preprint, 5 authors.	**time to viral-, 40.0% higher, relative time 1.40, *p* = 0.06**, treatment 18, control 19.
[Lora-Tamayo], 2/11/2021, retrospective, Spain, Europe, peer-reviewed, 10 authors.	**risk of death, 50.5% lower, RR 0.50, *p* < 0.001**, treatment 7,192, control 1,361, odds ratio converted to relative risk, univariate, control prevalence approximated with overall prevalence.
[Lotfy], 1/1/2021, retrospective, Saudi Arabia, Middle East, peer-reviewed, mean age 55.0, 3 authors, excluded in exclusion analyses: substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.	**risk of death, 24.8% higher, RR 1.25, *p* = 0.76**, treatment 6 of 99 (6.1%), control 5 of 103 (4.9%).
	risk of mechanical ventilation, 41.2% higher, RR 1.41, *p* = 0.34, treatment 19 of 99 (19.2%), control 14 of 103 (13.6%).
	risk of ICU admission, 16.5% higher, RR 1.17, *p* = 0.53, treatment 28 of 99 (28.3%), control 25 of 103 (24.3%).
[Luo], 6/17/2020, retrospective, USA, North America, peer-reviewed, 31 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	**risk of death, 2.2% higher, RR 1.02, *p* = 0.99**, treatment 11 of 35 (31.4%), control 4 of 13 (30.8%), odds ratio converted to relative risk.
[Luo (B)], 5/21/2020, retrospective, China, Asia, peer-reviewed, 9 authors.	**risk of death, 32.4% lower, RR 0.68, *p* = 0.72**, treatment 19, control 264, multivariate, RR approximated with OR.
[Lyngbakken], 7/17/2020, Randomized Controlled Trial, Norway, Europe, peer-reviewed, median age 62.0, 11 authors.	**risk of death, 3.7% lower, RR 0.96, *p* = 1.00**, treatment 1 of 27 (3.7%), control 1 of 26 (3.8%), NNT 702.
	improvement in viral load reduction rate, 71.0%

	lower, relative rate 0.29, *p* = 0.51, treatment 27, control 26.
[López], 11/2/2020, retrospective, Spain, Europe, peer-reviewed, 7 authors.	**risk of progression, 64.3% lower, RR 0.36, *p* = 0.02**, treatment 5 of 36 (13.9%), control 14 of 36 (38.9%), NNT 4.0.
[Magagnoli], 4/21/2020, retrospective, database analysis, USA, North America, peer-reviewed, 7 authors.	**risk of death, 11.0% lower, RR 0.89, *p* = 0.74**, treatment 39 of 148 (26.4%), control 18 of 163 (11.0%), adjusted per study, HCQ+AZ w/dispositions.
	risk of death, 1.0% lower, RR 0.99, *p* = 0.98, treatment 30 of 114 (26.3%), control 18 of 163 (11.0%), adjusted per study, HCQ w/dispositions.
	risk of death, 31.0% higher, RR 1.31, *p* = 0.28, treatment 49 of 214 (22.9%), control 37 of 395 (9.4%), adjusted per study, HCQ+AZ.
	risk of death, 83.0% higher, RR 1.83, *p* = 0.009, treatment 38 of 198 (19.2%), control 37 of 395 (9.4%), adjusted per study, HCQ.
[Mahévas], 5/14/2020, retrospective, France, Europe, peer-reviewed, 34 authors.	**risk of death, 20.0% higher, RR 1.20, *p* = 0.75**, treatment 9 of 84 (10.7%), control 8 of 89 (9.0%), adjusted per study.
[Maldonado], 11/5/2020, retrospective, Spain, Europe, peer-reviewed, 10 authors, excluded in exclusion analyses: treatment or control group size extremely small.	**risk of death, 90.9% lower, RR 0.09, *p* = 0.17**, treatment 1 of 11 (9.1%), control 1 of 1 (100.0%), NNT 1.1.
[Mallat], 5/2/2020, retrospective, Abu Dhabi, Middle East, peer-reviewed, 8 authors.	**time to viral-, 203.0% higher, relative time 3.03, *p* = 0.02**, treatment 23, control 11.
[Martin-Vicente], 3/8/2021, retrospective, Spain, Europe, preprint, 38 authors, excluded in exclusion analyses: unadjusted results with no group details, treatment or control group size extremely small.	**risk of death, 59.3% lower, RR 0.41, *p* = 0.41**, treatment 37 of 91 (40.7%), control 1 of 1 (100.0%), NNT 1.7.
[Martinez-Lopez], 6/30/2020, retrospective, Spain, Europe, peer-	**risk of death, 33.0% lower, RR 0.67, *p* = 0.20**, treatment 47 of 148 (31.8%), control 9 of 19

reviewed, median age 71.0, 25 authors.	(47.4%), NNT 6.4.
[Matangila], 12/18/2020, retrospective, DR Congo, Africa, peer-reviewed, median age 54.0, 12 authors.	risk of death, 54.9% lower, RR 0.45, p = 0.21, treatment 25 of 147 (17.0%), control 8 of 13 (61.5%), NNT 2.2, adjusted per study, odds ratio converted to relative risk.
[McGrail], 7/19/2020, retrospective, USA, North America, preprint, 2 authors, excluded in exclusion analyses: excessive unadjusted differences between groups.	risk of death, 70.0% higher, RR 1.70, p = 0.69, treatment 4 of 33 (12.1%), control 3 of 42 (7.1%).
[Membrillo de Novales], 5/5/2020, retrospective, Spain, Europe, preprint, 19 authors.	risk of death, 55.1% lower, RR 0.45, p = 0.002, treatment 27 of 123 (22.0%), control 21 of 43 (48.8%), NNT 3.7.
[Menardi], 9/30/2021, retrospective, Italy, Europe, peer-reviewed, 10 authors, excluded in exclusion analyses: excessive unadjusted differences between groups, substantial unadjusted confounding by indication likely.	risk of death, 35.2% lower, RR 0.65, p = 0.12, treatment 32 of 200 (16.0%), control 19 of 77 (24.7%), NNT 12.
[Mikami], 6/30/2020, retrospective, USA, North America, peer-reviewed, 7 authors.	risk of death, 47.0% lower, RR 0.53, p < 0.001, treatment 575 of 2,077 (27.7%), control 231 of 743 (31.1%), NNT 29, adjusted per study.
[Modrák], 12/4/2020, retrospective, Czech Republic, Europe, preprint, 26 authors.	risk of death, 59.0% lower, RR 0.41, p = 0.04, treatment 108, control 105, Cox (single).
[Mohandas], 4/26/2021, retrospective, India, South Asia, peer-reviewed, 6 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, unadjusted results with no group details, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	risk of death, 81.0% higher, RR 1.81, p = 0.007, treatment 27 of 384 (7.0%), control 115 of 2,961 (3.9%).
[Mulhem], 4/7/2021, retrospective, database analysis, USA, North America, peer-reviewed, 3 authors, excluded in exclusion analyses: substantial	risk of death, 28.3% higher, RR 1.28, p = 0.10, treatment 435 of 2,496 (17.4%), control 81 of 723 (11.2%), adjusted per study, odds ratio converted to relative risk, logistic regression.

unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	
[Nachega], 10/2/2020, retrospective, database analysis, DR Congo, Africa, peer-reviewed, median age 46.0, 25 authors.	**risk of death, 27.6% lower, RR 0.72, *p* = 0.17**, treatment 69 of 630 (11.0%), control 28 of 96 (29.2%), NNT 5.5, adjusted per study, odds ratio converted to relative risk.
	risk of no improvement, 25.8% lower, RR 0.74, *p* = 0.13, adjusted per study, odds ratio converted to relative risk.
[Naseem], 12/14/2020, retrospective, Pakistan, South Asia, preprint, 5 authors.	**risk of death, 33.3% lower, RR 0.67, *p* = 0.34**, treatment 77, control 1,137, multivariate Cox.
[Núñez-Gil], 11/9/2020, retrospective, database analysis, multiple countries, multiple regions, peer-reviewed, median age 68.0, 49 authors.	**risk of death, 7.9% lower, RR 0.92, *p* = 0.005**, treatment 200 of 686 (29.2%), control 100 of 268 (37.3%), NNT 12, adjusted per study, odds ratio converted to relative risk.
[Orioli], 12/14/2020, retrospective, Belgium, Europe, peer-reviewed, 9 authors.	**risk of death, 12.7% lower, RR 0.87, *p* = 1.00**, treatment 8 of 55 (14.5%), control 3 of 18 (16.7%), NNT 47.
[Ouedraogo], 2/5/2021, retrospective, Burkina Faso, Africa, peer-reviewed, 14 authors.	**risk of death, 33.0% lower, RR 0.67, *p* = 0.38**, treatment 397, control 59, multivariate.
	risk of ARDS, 68.0% lower, RR 0.32, *p* = 0.001, treatment 397, control 59, multivariate, RR approximated with OR.
[Ozturk], 12/4/2020, retrospective, Turkey, Europe, peer-reviewed, 70 authors.	**risk of death, 43.9% lower, RR 0.56, *p* = 0.14**, treatment 165 of 1,127 (14.6%), control 6 of 23 (26.1%), NNT 8.7, CQ/HCQ.
[Paccoud], 6/18/2020, retrospective, France, Europe, peer-reviewed, 20 authors.	**risk of death, 11.0% lower, RR 0.89, *p* = 0.88**, treatment 21 of 38 (55.3%), control 26 of 46 (56.5%), NNT 79, adjusted per study.
[Pasquini], 8/23/2020, retrospective, Italy, Europe, peer-reviewed, 9 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 16.4% lower, RR 0.84, *p* = 0.34**, treatment 23 of 33 (69.7%), control 15 of 18 (83.3%), NNT 7.3.

[Peng], 12/4/2020, retrospective, China, Asia, peer-reviewed, 21 authors.	**risk of progression, 10.8% lower, RR 0.89, p = 0.63**, treatment 29 of 453 (6.4%), control 256 of 3,567 (7.2%), NNT 129, CQ/HCQ risk of AKI.
[Peters], 8/15/2020, retrospective, Netherlands, Europe, peer-reviewed, 21 authors, excluded in exclusion analyses: excessive unadjusted differences between groups.	**risk of death, 9.0% higher, RR 1.09, p = 0.57**, treatment 419 of 1,596 (26.3%), control 53 of 353 (15.0%), adjusted per study.
[Pinato], 8/18/2020, retrospective, multiple countries, multiple regions, peer-reviewed, 64 authors.	**risk of death, 59.0% lower, RR 0.41, p < 0.001**, treatment 30 of 182 (16.5%), control 181 of 446 (40.6%), NNT 4.1.
[Psevdos], 12/31/2020, retrospective, USA, North America, peer-reviewed, 3 authors, excluded in exclusion analyses: unadjusted results with no group details, no treatment details, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.	**risk of death, 63.5% higher, RR 1.63, p = 0.52**, treatment 17 of 52 (32.7%), control 3 of 15 (20.0%).
[Purwati], 2/9/2021, Double Blind Randomized Controlled Trial, Indonesia, South Asia, peer-reviewed, 12 authors.	**risk of no virological cure, 66.3% lower, RR 0.34, p < 0.001**, treatment 38 of 121 (31.4%), control 111 of 119 (93.3%), NNT 1.6, day 7.
[Qin], 11/23/2020, retrospective, China, Asia, peer-reviewed, 17 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 34.3% lower, RR 0.66, p = 0.61**, treatment 3 of 43 (7.0%), control 75 of 706 (10.6%), NNT 27.
[Ramírez-García], 5/31/2021, retrospective, Spain, Europe, peer-reviewed, 5 authors, excluded in exclusion analyses: excessive unadjusted differences between groups, substantial unadjusted confounding by indication likely.	**risk of death, 67.0% lower, RR 0.33, p < 0.001**, treatment 48 of 350 (13.7%), control 22 of 53 (41.5%), NNT 3.6.
	risk of ICU admission, 6.0% higher, RR 1.06, p = 1.00, treatment 35 of 350 (10.0%), control 5 of 53 (9.4%).
[RECOVERY], 6/5/2020, Randomized Controlled Trial, United Kingdom, Europe, preprint, 29 authors, excluded in	**risk of death, 9.0% higher, RR 1.09, p = 0.15**, treatment 421 of 1,561 (27.0%), control 790 of 3,155 (25.0%).

exclusion analyses: excessive dosage in late stage patients, results do not apply to typical dosages.	
[Reis], 4/22/2021, Double Blind Randomized Controlled Trial, Brazil, South America, peer-reviewed, 18 authors, dosage 800mg day 1, 400mg days 2-10.	**risk of death, 66.0% lower, RR 0.34, *p* = 1.00**, treatment 0 of 214 (0.0%), control 1 of 227 (0.4%), NNT 227, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 24.0% lower, RR 0.76, *p* = 0.57, treatment 8 of 214 (3.7%), control 11 of 227 (4.8%), NNT 90, ITT, Cox proportional hazards.
	risk of no virological cure, 4.1% lower, RR 0.96, *p* = 0.10, treatment 97 of 185 (52.4%), control 102 of 179 (57.0%), NNT 22, adjusted per study, odds ratio converted to relative risk, ITT, mixed-effect logistic model.
[Rivera], 7/22/2020, retrospective, USA, North America, peer-reviewed, 45 authors.	**risk of death, 2.4% higher, RR 1.02, *p* = 0.92**, treatment 44 of 179 (24.6%), control 59 of 327 (18.0%), adjusted per study, odds ratio converted to relative risk.
[Rivera-Izquierdo], 7/9/2020, retrospective, Spain, Europe, peer-reviewed, 21 authors.	**risk of death, 19.0% lower, RR 0.81, *p* = 0.75**, treatment 215, control 23.
[Rodriguez], 11/9/2020, prospective, Spain, Europe, peer-reviewed, 13 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 59.0% lower, RR 0.41, *p* = 0.23**, treatment 8 of 39 (20.5%), control 2 of 4 (50.0%), NNT 3.4.
[Rodriguez-Gonzalez], 11/28/2020, retrospective, Spain, Europe, peer-reviewed, 20 authors.	**risk of death, 22.8% lower, RR 0.77, *p* = 0.26**, treatment 251 of 1,148 (21.9%), control 17 of 60 (28.3%), NNT 15.
[Rodriguez-Nava], 11/5/2020, retrospective, USA, North America, peer-reviewed, median age 68.0, 8 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, excessive unadjusted differences between groups, unadjusted results with no group details.	**risk of death, 6.3% higher, RR 1.06, *p* = 0.77**, treatment 22 of 65 (33.8%), control 79 of 248 (31.9%), unadjusted.

[Rogado], 5/29/2020, retrospective, Spain, Europe, peer-reviewed, 9 authors.	**risk of death, 91.6% lower, RR 0.08, *p* = 0.02**, treatment 1 of 8 (12.5%), control 7 of 9 (77.8%), NNT 1.5, odds ratio converted to relative risk, multivariate logistic regression.
[Roger], 7/10/2021, prospective, France, Europe, peer-reviewed, 34 authors, excluded in exclusion analyses: substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	**risk of death, no change, RR 1.00, *p* = 0.94**, treatment 53 of 289 (18.3%), control 120 of 677 (17.7%), odds ratio converted to relative risk.
[Roig], 1/31/2021, retrospective, Spain, Europe, peer-reviewed, 6 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 15.6% lower, RR 0.84, *p* = 0.76**, treatment 33 of 67 (49.3%), control 7 of 12 (58.3%), NNT 11.
[Roomi], 8/13/2020, retrospective, USA, North America, peer-reviewed, 11 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	**risk of death, 37.7% higher, RR 1.38, *p* = 0.54**, treatment 13 of 144 (9.0%), control 6 of 32 (18.8%), NNT 10, adjusted per study, odds ratio converted to relative risk.
[Rosenberg], 5/11/2020, retrospective, USA, North America, peer-reviewed, 14 authors.	**risk of death, 35.0% higher, RR 1.35, *p* = 0.31**, treatment 189 of 735 (25.7%), control 28 of 221 (12.7%), adjusted per study.
[Réa-Neto], 4/27/2021, Randomized Controlled Trial, Brazil, South America, peer-reviewed, 6 authors.	**risk of death, 57.0% higher, RR 1.57, *p* = 0.20**, treatment 16 of 53 (30.2%), control 10 of 52 (19.2%).
	risk of mechanical ventilation, 115.0% higher, RR 2.15, *p* = 0.03, treatment 53, control 52.
	9-point scale clinical status, 147.0% higher, RR 2.47, *p* = 0.02, treatment 53, control 52, RR approximated with OR.
[Saib], 6/9/2021, prospective, propensity score matching, France, Europe, peer-reviewed, 9 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	**risk of death/intubation, 125.0% higher, RR 2.25, *p* = 0.23**, treatment 9 of 52 (17.3%), control 4 of 52 (7.7%), PSM.

[Salazar], 11/4/2020, retrospective, USA, North America, peer-reviewed, 19 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, unadjusted results with no group details.	**risk of death, 37.0% higher, RR 1.37, p = 0.28**, treatment 12 of 92 (13.0%), control 80 of 811 (9.9%).
[Saleemi], 8/11/2020, retrospective, Saudi Arabia, Middle East, preprint, 5 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	**median time to PCR-, 21.0% higher, relative time 1.21, p < 0.05**, treatment 65, control 20.
[Salvador], 3/4/2021, prospective, Portugal, Europe, peer-reviewed, 10 authors.	**risk of death, 32.9% lower, RR 0.67, p = 0.10**, treatment 28 of 121 (23.1%), control 58 of 124 (46.8%), NNT 4.2, odds ratio converted to relative risk, multivariate.
	risk of mechanical ventilation, 447.8% higher, RR 5.48, p = 0.003, treatment 32 of 121 (26.4%), control 12 of 124 (9.7%), odds ratio converted to relative risk, multivariate.
	risk of death/intubation, 16.7% lower, RR 0.83, p = 0.21, treatment 51 of 121 (42.1%), control 63 of 124 (50.8%), NNT 12, odds ratio converted to relative risk, univariate.
[Sammartino], 5/10/2021, retrospective, propensity score matching, USA, North America, peer-reviewed, 7 authors, excluded in exclusion analyses: substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	**risk of death, 240.0% higher, RR 3.40, p = 0.002**, treatment 137, control 191, PSM, model 1a, RR approximated with OR.
[Sands], 1/1/2021, retrospective, database analysis, USA, North America, peer-reviewed, 10 authors, excluded in exclusion analyses: includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons, substantial unadjusted confounding by indication likely.	**risk of death, 69.9% higher, RR 1.70, p = 0.01**, treatment 101 of 973 (10.4%), control 56 of 696 (8.0%), odds ratio converted to relative risk.

[Sarfaraz], 1/2/2021, retrospective, Pakistan, South Asia, preprint, 7 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, significant unadjusted confounding possible, unadjusted results with no group details.	**risk of death, 45.0% higher, RR 1.45, p = 0.07**, treatment 40 of 94 (42.6%), control 27 of 92 (29.3%).
[Sarhan], 11/2/2021, Randomized Controlled Trial, Egypt, Africa, peer-reviewed, 8 authors, 1 October, 2020 - 10 March, 2021, this trial compares with another treatment - results may be better when compared to placebo, excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline, significant unadjusted differences between groups.	**risk of death, 25.7% lower, RR 0.74, p = 0.39**, treatment 12 of 56 (21.4%), control 15 of 52 (28.8%), NNT 13.
	risk of no hospital discharge, 25.7% lower, RR 0.74, p = 0.39, treatment 12 of 56 (21.4%), control 15 of 52 (28.8%), NNT 13.
	hospitalization time, 25.0% higher, relative time 1.25, p = 0.06, treatment 56, control 52.
[Sbidian], 6/19/2020, retrospective, database analysis, France, Europe, preprint, 21 authors, excluded in exclusion analyses: significant issues found with adjustments.	**risk of death, 5.0% higher, RR 1.05, p = 0.74**, treatment 111 of 623 (17.8%), control 830 of 3,792 (21.9%), NNT 25, adjusted per study, whole population HCQ AIPTW adjusted.
	risk of no hospital discharge, 20.0% lower, RR 0.80, p = 0.002, treatment 623, control 3,792, adjusted per study, whole population HCQ AIPTW adjusted.
[Schwartz], 6/18/2021, Double Blind Randomized Controlled Trial, Canada, North America, peer-reviewed, 20 authors, dosage 800mg day 1, 400mg days 2-5.	**risk of ICU admission, 133.3% higher, RR 2.33, p = 1.00**, treatment 1 of 111 (0.9%), control 0 of 37 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of hospitalization, 533.3% higher, RR 6.33, p = 0.57, treatment 4 of 111 (3.6%), control 0 of 37 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of ICU admission, 141.9% higher, RR 2.42, p = 1.00, treatment 1 of 74 (1.4%), control 0 of 31 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), per-protocol.
	risk of hospitalization, 141.9% higher, RR 2.42, p = 1.00, treatment 1 of 74 (1.4%), control 0 of 31 (0.0%), continuity correction due to zero event

	(with reciprocal of the contrasting arm), per-protocol.
[Self], 11/9/2020, Randomized Controlled Trial, USA, North America, peer-reviewed, 33 authors.	**risk of death, 6.2% higher, RR 1.06, p = 0.85**, treatment 25 of 241 (10.4%), control 25 of 236 (10.6%), NNT 455, adjusted per study, odds ratio converted to relative risk.
[Serrano], 9/22/2020, retrospective, Spain, Europe, peer-reviewed, 8 authors.	**risk of death, 43.0% lower, RR 0.57, p = 0.14**, treatment 6 of 14 (42.9%), control 6 of 8 (75.0%), NNT 3.1.
[Shabrawishi], 5/11/2020, retrospective, Saudi Arabia, Middle East, preprint, mean age 43.9, 5 authors.	**risk of no virological cure at day 5, 14.7% lower, RR 0.85, p = 0.66**, treatment 12 of 45 (26.7%), control 15 of 48 (31.2%), NNT 22.
[Sheshah], 11/13/2020, retrospective, Saudi Arabia, Middle East, peer-reviewed, 8 authors.	**risk of death, 80.0% lower, RR 0.20, p < 0.001**, treatment 267, control 33, odds ratio converted to relative risk.
[Shoaibi], 9/24/2020, retrospective, database analysis, USA, North America, preprint, 5 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 15.4% lower, RR 0.85, p < 0.001**, treatment 686 of 5,047 (13.6%), control 3,923 of 24,404 (16.1%), NNT 40.
[Signes-Costa], 12/16/2020, retrospective, multiple countries, multiple regions, peer-reviewed, 28 authors.	**risk of death, 47.0% lower, RR 0.53, p < 0.001**, treatment 4,854, control 993, adjusted per study.
[Singh (B)], 6/8/2021, Randomized Controlled Trial, India, South Asia, preprint, 13 authors, this trial uses multiple treatments in the treatment arm (combined with ribavirin) - results of individual treatments may vary.	**risk of death, 47.5% lower, RR 0.53, p = 0.45**, treatment 3 of 20 (15.0%), control 6 of 21 (28.6%), NNT 7.4, severe.
	risk of death, 50.0% lower, RR 0.50, p = 0.48, treatment 3 of 37 (8.1%), control 6 of 37 (16.2%), NNT 12, all patients.
	risk of no recovery, 14.1% lower, RR 0.86, p = 0.76, treatment 9 of 20 (45.0%), control 11 of 21 (52.4%), NNT 14, severe.
	risk of no recovery, 8.3% lower, RR 0.92, p = 1.00, treatment 11 of 37 (29.7%), control 12 of 37 (32.4%), NNT 37, all patients.
[Singh], 5/19/2020, retrospective,	**risk of death, 5.0% lower, RR 0.95, p = 0.72**,

database analysis, USA, North America, preprint, 4 authors, excluded in exclusion analyses: confounding by indication is likely and adjustments do not consider COVID-19 severity.	treatment 104 of 910 (11.4%), control 109 of 910 (12.0%), NNT 182.
	risk of mechanical ventilation, 19.0% lower, RR 0.81, *p* = 0.26, treatment 46 of 910 (5.1%), control 57 of 910 (6.3%), NNT 83.
[Sivapalan], 6/3/2021, Double Blind Randomized Controlled Trial, Denmark, Europe, peer-reviewed, 32 authors.	**risk of death, 92.0% lower, RR 0.08, *p* = 0.32**, treatment 1 of 61 (1.6%), control 2 of 56 (3.6%), NNT 52, adjusted per study.
	risk of ICU admission, 22.4% higher, RR 1.22, *p* = 1.00, treatment 4 of 61 (6.6%), control 3 of 56 (5.4%).
	relative days alive and discharged from hospital within 14 days (inverse), 8.4% worse, RR 1.08, *p* = 0.36, treatment 61, control 56, adjusted per study.
[Smith], 5/31/2021, retrospective, USA, North America, preprint, 4 authors, excluded in exclusion analyses: immortal time bias may significantly affect results.	**risk of death, 27.2% lower, RR 0.73, *p* = 0.002**, treatment 19 of 37 (51.4%), control 182 of 218 (83.5%), NNT 3.1, odds ratio converted to relative risk, >3g HCQ and >1g AZ, multivariable cox proportional hazard regression.
[Solh], 10/20/2020, retrospective, database analysis, USA, North America, preprint, 5 authors, excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline, substantial unadjusted confounding by indication likely.	**risk of death, 18.0% higher, RR 1.18, *p* = 0.17**, treatment 131 of 265 (49.4%), control 134 of 378 (35.4%), adjusted per study.
[SOLIDARITY], 10/15/2020, Randomized Controlled Trial, multiple countries, multiple regions, peer-reviewed, baseline oxygen requirements 64.0%, 15 authors, excluded in exclusion analyses: excessive dosage in late stage patients, results do not apply to typical dosages, very late stage, >50% on oxygen/ventilation at baseline.	**risk of death, 19.0% higher, RR 1.19, *p* = 0.23**, treatment 104 of 947 (11.0%), control 84 of 906 (9.3%).
[Sosa-García], 6/29/2020, retrospective, Mexico, North America, peer-reviewed, baseline oxygen requirements 100.0%, 6 authors, excluded in exclusion analyses:	**risk of death, 10.5% higher, RR 1.11, *p* = 1.00**, treatment 7 of 38 (18.4%), control 3 of 18 (16.7%).

very late stage, >50% on oxygen/ventilation at baseline, substantial unadjusted confounding by indication likely.	
[Soto-Becerra], 10/8/2020, retrospective, database analysis, Peru, South America, preprint, median age 59.4, 4 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	**risk of death, 18.1% lower, RR 0.82, $p < 0.001$**, treatment 346 of 692 (50.0%), control 1,606 of 2,630 (61.1%), NNT 9.0, day 54 (last day available) weighted KM.
	risk of death, 84.0% higher, RR 1.84, $p = 0.02$, treatment 165 of 692 (23.8%), control 401 of 2,630 (15.2%), adjusted per study, day 30.
[Stewart], 3/17/2021, retrospective, USA, North America, peer-reviewed, 37 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	**risk of death, 18.0% higher, RR 1.18, $p = 0.27$**, treatment 90 of 429 (21.0%), control 141 of 737 (19.1%), adjusted per study, VA, HCQ+AZ.
[Stewart (B)], 3/17/2021, retrospective, USA, North America, peer-reviewed, 37 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	**risk of mechanical ventilation, 29.0% higher, RR 1.29, $p = 0.09$**, treatment 48 of 305 (15.7%), control 95 of 1,302 (7.3%), adjusted per study, Aetion, HCQ.
[Stewart (C)], 3/17/2021, retrospective, USA, North America, peer-reviewed, 37 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic	**risk of death, 16.0% higher, RR 1.16, $p = 0.26$**, treatment 428 of 1,711 (25.0%), control 123 of 688 (17.9%), adjusted per study, COTA/HMH, HCQ+AZ.

when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	
[Stewart (D)], 3/17/2021, retrospective, USA, North America, peer-reviewed, 37 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	risk of death, 90.0% higher, RR 1.90, p = 0.09, treatment 46 of 208 (22.1%), control 47 of 1,334 (3.5%), adjusted per study, Dascena, HCQ+AZ.
[Stewart (E)], 3/17/2021, retrospective, USA, North America, peer-reviewed, 37 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	risk of death, 9.0% higher, RR 1.09, p = 0.65, treatment 212 of 1,157 (18.3%), control 203 of 1,101 (18.4%), NNT 873, adjusted per study, Health Catalyst, HCQ+AZ.
[Stewart (F)], 3/17/2021, retrospective, USA, North America, peer-reviewed, 37 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	risk of death, 129.9% higher, RR 2.30, p < 0.001, treatment 32 of 108 (29.6%), control 33 of 256 (12.9%), Synapse, HCQ+AZ.
[Stewart (G)], 3/17/2021, retrospective, USA, North America, peer-reviewed, 37	risk of death, 1.0% lower, RR 0.99, p = 0.95, treatment 66 of 578 (11.4%), control 188 of 1,243

authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	(15.1%), NNT 27, adjusted per study, TriNetX, HCQ+AZ.
[Synolaki], 9/5/2020, retrospective, Greece, Europe, preprint, 20 authors.	risk of death, 23.6% lower, RR 0.76, p = 0.27, treatment 21 of 98 (21.4%), control 60 of 214 (28.0%), NNT 15.
[Sánchez-Álvarez], 4/27/2020, retrospective, database analysis, Spain, Europe, peer-reviewed, mean age 67.0, 10 authors.	risk of death, 45.9% lower, RR 0.54, p = 0.005, treatment 322, control 53, odds ratio converted to relative risk.
[Taccone], 12/23/2020, retrospective, Belgium, Europe, peer-reviewed, 10 authors.	risk of death, 24.7% lower, RR 0.75, p = 0.02, treatment 449 of 1,308 (34.3%), control 183 of 439 (41.7%), NNT 14, odds ratio converted to relative risk.
[Taieb], 6/30/2021, retrospective, Senegal, Africa, peer-reviewed, 29 authors.	risk of no hospital discharge, 38.7% lower, RR 0.61, p = 0.02, treatment 674, control 252, multivariate, RR approximated with OR.
[Tan], 12/14/2020, retrospective, China, Asia, peer-reviewed, 7 authors.	hospitalization time, 35.2% lower, relative time 0.65, p = 0.04, treatment 8, control 277.
[Tang], 4/14/2020, Randomized Controlled Trial, China, Asia, peer-reviewed, 24 authors.	risk of no virological cure at day 21, 21.4% lower, RR 0.79, p = 0.51, treatment 11 of 75 (14.7%), control 14 of 75 (18.7%), NNT 25.
[Tehrani], 10/30/2020, retrospective, Sweden, Europe, peer-reviewed, 5 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, unadjusted results with no group details.	risk of death, 13.4% lower, RR 0.87, p = 0.63, treatment 16 of 65 (24.6%), control 54 of 190 (28.4%), NNT 26.
[Texeira], 12/31/2020, retrospective, USA, North America, peer-reviewed, 6 authors, excluded in exclusion analyses: unadjusted results with no group details,	risk of death, 79.3% higher, RR 1.79, p = 0.10, treatment 17 of 65 (26.2%), control 14 of 96 (14.6%).

no treatment details, substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.	
[Thompson], 2/9/2021, Double Blind Randomized Controlled Trial, USA, North America, preprint, 1 author.	**risk of death, 6.2% higher, RR 1.06, p = 0.85**, treatment 25 of 241 (10.4%), control 25 of 236 (10.6%), NNT 455, adjusted per study, odds ratio converted to relative risk, day 28.
	risk of death, 51.0% higher, RR 1.51, p = 0.28, treatment 18 of 241 (7.5%), control 14 of 236 (5.9%), adjusted per study, odds ratio converted to relative risk, day 14.
	risk of 7-point scale, 3.1% higher, RR 1.03, p = 0.87, treatment 241, control 236, day 28, RR approximated with OR.
	risk of 7-point scale, 2.0% lower, RR 0.98, p = 0.91, treatment 241, control 236, day 14, RR approximated with OR.
[Trullàs], 7/14/2020, retrospective, Spain, Europe, preprint, median age 75.0, 8 authors.	**risk of death, 35.6% lower, RR 0.64, p = 0.12**, treatment 20 of 66 (30.3%), control 16 of 34 (47.1%), NNT 6.0.
[Turrini], 6/11/2021, retrospective, Italy, Europe, peer-reviewed, 16 authors.	**risk of death, 9.8% lower, RR 0.90, p = 0.15**, treatment 103 of 160 (64.4%), control 33 of 45 (73.3%), NNT 11, adjusted per study, odds ratio converted to relative risk, multivariate.
[Ubaldo], 2/1/2021, retrospective, Philippines, Asia, peer-reviewed, 3 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, very late stage, ICU patients, unadjusted results with no group details.	**risk of death, 18.4% lower, RR 0.82, p = 0.64**, treatment 17 of 25 (68.0%), control 5 of 6 (83.3%), NNT 6.5, COVID-19 positive patients.
[Ulrich], 9/23/2020, Randomized Controlled Trial, USA, North America, peer-reviewed, baseline oxygen requirements 63.3%, mean age 66.2, 18	**risk of death, 6.0% higher, RR 1.06, p = 1.00**, treatment 7 of 67 (10.4%), control 6 of 61 (9.8%).

authors, excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline.	
[Uygen], 9/15/2021, retrospective, Turkey, Europe, peer-reviewed, 4 authors.	**time to viral-, 12.2% lower, relative time 0.88, p = 0.05**, treatment 15, control 25.
[van Halem], 11/27/2020, retrospective, Belgium, Europe, peer-reviewed, 10 authors.	**risk of death, 31.6% lower, RR 0.68, p = 0.05**, treatment 34 of 164 (20.7%), control 47 of 155 (30.3%), NNT 10. With the observed event rates, ~3 more patients per arm would result in statistical significance.
[Vernaz], 12/31/2020, retrospective, propensity score matching, Switzerland, Europe, peer-reviewed, 15 authors, excluded in exclusion analyses: substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically, substantial unadjusted confounding by indication likely.	**risk of death, 15.3% lower, RR 0.85, p = 0.71**, treatment 12 of 93 (12.9%), control 16 of 105 (15.2%), NNT 43, HCQ vs. SOC, PSM.
	hospitalization time, 49.0% higher, relative time 1.49, p = 0.002, treatment 93, control 105, HCQ vs. SOC, PSM.
[Wang], 6/10/2020, retrospective, database analysis, USA, North America, preprint, 3 authors, excluded in exclusion analyses: confounding by indication is likely and adjustments do not consider COVID-19 severity.	**risk of death, 5.8% lower, RR 0.94, p = 0.63**, treatment 1,866, control 5,726, odds ratio converted to relative risk.
[Xia], 2/11/2020, retrospective, China, Asia, preprint, 1 author, excluded in exclusion analyses: minimal details provided.	**risk of no virological cure, 37.5% lower, RR 0.62, p = 0.17**, treatment 5 of 10 (50.0%), control 12 of 15 (80.0%), NNT 3.3.
[Yegerov], 1/8/2021, retrospective, Kazakhstan, Asia, preprint, 8 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 95.3% lower, RR 0.05, p = 1.00**, treatment 0 of 23 (0.0%), control 20 of 1,049 (1.9%), NNT 52, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
[Yu (B)], 8/3/2020, retrospective, China, Asia, preprint, median age 62.0, 6 authors.	**risk of progression to critical, 82.5% lower, RR 0.17, p = 0.049**, treatment 1 of 231 (0.4%), control 32 of 1,291 (2.5%), NNT 49, baseline critical cohort reported separately in Yu et al..

	risk of death, 85.0% lower, RR 0.15, *p* = 0.02, treatment 1 of 73 (1.4%), control 238 of 2,604 (9.1%), NNT 13, HCQ treatment started early vs. non-HCQ.
[Yu (C)], 5/15/2020, retrospective, China, Asia, peer-reviewed, 8 authors.	**risk of death, 60.5% lower, RR 0.40, *p* = 0.002**, treatment 9 of 48 (18.8%), control 238 of 502 (47.4%), NNT 3.5.
[Zhong], 3/26/2020, retrospective, China, Asia, preprint, 1 author.	**risk of no virological cure at day 10, 80.0% lower, RR 0.20, *p* < 0.001**, treatment 5 of 115 (4.3%), control 17 of 82 (20.7%), NNT 6.1, adjusted per study.
[Águila-Gordo], 11/11/2020, retrospective, Spain, Europe, peer-reviewed, mean age 84.4, 6 authors.	**risk of death, 67.0% lower, RR 0.33, *p* = 0.10**, treatment 151 of 346 (43.6%), control 47 of 70 (67.1%), NNT 4.3, adjusted per study.
[Çivriz Bozdağ], 9/15/2021, retrospective, Turkey, Europe, peer-reviewed, 62 authors, excluded in exclusion analyses: substantial time varying confounding likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	**risk of death, 399.2% higher, RR 4.99, *p* = 0.003**, treatment 35, control 140.
[Çiyiltepe], 4/30/2021, retrospective, Turkey, Europe, peer-reviewed, 5 authors, excluded in exclusion analyses: treatment group only includes patients where treatment failed resulting in ICU admission.	**risk of death, 3.2% lower, RR 0.97, *p* = 0.85**, treatment 69 of 95 (72.6%), control 39 of 52 (75.0%), NNT 42.
[Ñamendys-Silva], 10/21/2020, retrospective, database analysis, Mexico, North America, peer-reviewed, mean age 57.3, 18 authors.	**risk of death, 32.3% lower, RR 0.68, *p* = 0.18**, treatment 24 of 54 (44.4%), control 42 of 64 (65.6%), NNT 4.7, HCQ+AZ vs. neither HCQ or CQ.
	risk of death, 37.1% lower, RR 0.63, *p* = 0.09, treatment 19 of 46 (41.3%), control 42 of 64 (65.6%), NNT 4.1, CQ vs. neither HCQ or CQ.
	risk of death, 34.5% lower, RR 0.66, *p* = 0.006, treatment 43 of 100 (43.0%), control 42 of 64 (65.6%), NNT 4.4, HCQ+AZ or CQ.

Pre-Exposure Prophylaxis

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. Only the first (most serious) outcome is used in pooled analysis, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

[Abella], 9/30/2020, Randomized Controlled Trial, USA, North America, peer-reviewed, 18 authors.	**risk of case, 5.0% lower, RR 0.95, *p* = 1.00**, treatment 4 of 64 (6.2%), control 4 of 61 (6.6%), NNT 325.
[Agarwal], 9/14/2021, prospective, India, South Asia, preprint, 1 author.	**risk of hospitalization, 94.8% lower, RR 0.05, *p* = 0.61**, treatment 0 of 29 (0.0%), control 17 of 455 (3.7%), NNT 27, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	relative severity, 26.9% better, RR 0.73, *p* = 0.21, treatment 29, control 455.
	risk of case, 4.6% higher, RR 1.05, *p* = 0.81, treatment 6 of 29 (20.7%), control 90 of 455 (19.8%).
[Ahmed], 11/23/2021, retrospective, Saudi Arabia, Middle East, peer-reviewed, 7 authors.	**risk of case, 99.3% lower, RR 0.007, *p* = 0.08**, treatment 0 of 50 (0.0%) cases, 13 of 50 (26.0%) controls, NNT 1.7, case control OR.
[Alegiani], 4/15/2021, retrospective, case control, database analysis, Italy, Europe, peer-reviewed, 16 authors.	**risk of death, 8.0% higher, RR 1.08, *p* = 0.64**, HCQ vs. other cDMARDs, RR approximated with OR.
	risk of hospitalization, 18.0% lower, RR 0.82, *p* = 0.03, HCQ vs. other cDMARDs, RR approximated with OR.
	risk of death, 19.0% higher, RR 1.19, *p* = 0.32, HCQ vs. MTX, RR approximated with OR.
	risk of hospitalization, 12.0% lower, RR 0.88, *p* = 0.17, HCQ vs. MTX, RR approximated with OR.
[Alzahrani], 4/15/2021, retrospective, Saudi Arabia, Middle East, peer-reviewed, 3 authors.	**risk of death, 58.7% lower, RR 0.41, *p* = 1.00**, treatment 0 of 14 (0.0%), control 1 of 33 (3.0%), NNT 33, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).

	risk of mechanical ventilation, 81.0% lower, RR 0.19, *p* = 0.54, treatment 0 of 14 (0.0%), control 3 of 33 (9.1%), NNT 11, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of severe case, 32.7% lower, RR 0.67, *p* = 0.70, treatment 2 of 14 (14.3%), control 7 of 33 (21.2%), NNT 14.
[Arleo], 10/27/2020, retrospective, USA, North America, preprint, 5 authors.	**risk of death, 50.0% lower, RR 0.50, *p* = 0.67**, treatment 1 of 20 (5.0%), control 5 of 50 (10.0%), NNT 20, all patients.
	risk of death, 52.0% lower, RR 0.48, *p* = 0.64, treatment 1 of 10 (10.0%), control 5 of 24 (20.8%), NNT 9.2, inpatients.
[Badyal], 6/7/2021, prospective, India, South Asia, peer-reviewed, 18 authors.	**risk of case, 60.1% lower, RR 0.40, *p* < 0.001**, treatment 247 of 617 (40.0%), control 611 of 1,473 (41.5%), NNT 69, adjusted per study, odds ratio converted to relative risk, >=6 weeks, logistic regression.
	risk of case, 35.1% lower, RR 0.65, *p* = 0.003, treatment 88 of 185 (47.6%), control 611 of 1,473 (41.5%), adjusted per study, odds ratio converted to relative risk, 4-5 weeks, logistic regression.
	risk of case, 23.2% lower, RR 0.77, *p* = 0.04, treatment 80 of 181 (44.2%), control 611 of 1,473 (41.5%), adjusted per study, odds ratio converted to relative risk, 2-3 weeks, logistic regression.
[Bae], 2/20/2021, retrospective, propensity score matching, South Korea, Asia, peer-reviewed, 8 authors.	**risk of case, 30.3% lower, RR 0.70, *p* = 0.18**, treatment 16 of 743 (2.2%), control 91 of 2,698 (3.4%), NNT 82, odds ratio converted to relative risk, PSM.
	risk of case, 19.5% lower, RR 0.81, *p* = 0.50, treatment 16 of 743 (2.2%), control 91 of 2,698 (3.4%), NNT 82, odds ratio converted to relative risk, PSM, adjusted for region.
	risk of case, 30.3% lower, RR 0.70, *p* = 0.30, treatment 16 of 743 (2.2%), control 91 of 2,698 (3.4%), NNT 82, odds ratio converted to relative

	risk, PSM, adjusted for immunosuppresant use.
	risk of case, 40.2% lower, RR 0.60, *p* = 0.09, odds ratio converted to relative risk, PSM, HCQ >= 6 months.
[Behera], 11/3/2020, retrospective, India, South Asia, peer-reviewed, 13 authors.	**risk of case, 27.9% lower, RR 0.72, *p* = 0.29**, treatment 7 of 19 (36.8%), control 179 of 353 (50.7%), NNT 7.2, adjusted per study, odds ratio converted to relative risk, model 2 conditional logistic regression.
	risk of case, 26.3% lower, RR 0.74, *p* = 0.25, treatment 7 of 19 (36.8%), control 179 of 353 (50.7%), NNT 7.2, odds ratio converted to relative risk, matched pair analysis.
[Bhatt], 8/4/2021, prospective, India, South Asia, preprint, 4 authors.	**risk of case, 49.3% higher, RR 1.49, *p* = 0.02**, treatment 167 of 731 (22.8%), control 30 of 196 (15.3%).
[Bhattacharya], 6/9/2020, retrospective, India, South Asia, preprint, 7 authors.	**risk of case, 80.7% lower, RR 0.19, *p* = 0.001**, treatment 4 of 54 (7.4%), control 20 of 52 (38.5%), NNT 3.2.
[Cassione], 5/12/2020, retrospective, Italy, Europe, preprint, survey, median age 52.5, 6 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of case, 49.6% higher, RR 1.50, *p* = 0.59**, treatment 10 of 127 (7.9%), control 2 of 38 (5.3%).
[Chatterjee], 5/28/2020, retrospective, India, South Asia, peer-reviewed, survey, 11 authors.	**risk of case, 66.8% lower, RR 0.33, *p* < 0.001**, treatment 12 of 68 (17.6%), control 206 of 387 (53.2%), NNT 2.8, full course vs. unused.
[Cordtz], 12/28/2020, retrospective, population-based cohort, Denmark, Europe, peer-reviewed, 10 authors.	**risk of hospitalization, 24.0% lower, RR 0.76, *p* = 0.67**, treatment 3 of 2,722 (0.1%), control 38 of 26,718 (0.1%), NNT 3124, adjusted per study, time-dependent exposure model.
	risk of hospitalization, 55.0% lower, RR 0.45, *p* = 0.28, treatment 3 of 2,722 (0.1%), control 38 of 26,718 (0.1%), NNT 3124, adjusted per study, time-fixed exposure model.
[Datta], 11/6/2020, retrospective, India,	**risk of case, 22.1% lower, RR 0.78, *p* = 0.47**,

South Asia, peer-reviewed, 7 authors.	treatment 16 of 146 (11.0%), control 19 of 135 (14.1%), NNT 32.
[de la Iglesia], 9/2/2020, retrospective, database analysis, Spain, Europe, preprint, 17 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of hospitalization, 50.0% higher, RR 1.50, *p* = 1.00**, treatment 3 of 687 (0.4%), control 2 of 688 (0.3%).
	risk of case, 42.6% higher, RR 1.43, *p* = 0.15, treatment 42 of 648 (6.5%), control 30 of 660 (4.5%), suspected COVID-19.
	risk of case, 7.8% lower, RR 0.92, *p* = 0.84, treatment 12 of 678 (1.8%), control 13 of 677 (1.9%), NNT 665, confirmed COVID-19.
[Desbois], 7/20/2020, retrospective, France, Europe, preprint, mean age 58.8, 13 authors.	**risk of case, 16.9% lower, RR 0.83, *p* = 1.00**, treatment 3 of 27 (11.1%), control 23 of 172 (13.4%), NNT 44.
[Dev], 3/24/2021, retrospective, India, South Asia, peer-reviewed, 5 authors.	**risk of case, 26.0% lower, RR 0.74, *p* = 0.003**, treatment 260, control 499, any number of HCQ doses vs. no HCQ prophylaxis.
[Ferreira (B)], 6/29/2020, retrospective, population-based cohort, database analysis, Portugal, Europe, peer-reviewed, 3 authors.	**risk of case, 47.1% lower, RR 0.53, *p* < 0.001**, NNT 67, adjusted per study, odds ratio converted to relative risk.
[Ferri], 8/27/2020, retrospective, Italy, Europe, peer-reviewed, survey, 29 authors.	**risk of COVID-19 case, 63.0% lower, RR 0.37, *p* = 0.01**, treatment 9 of 994 (0.9%), control 16 of 647 (2.5%), NNT 64.
[Fitzgerald], 2/5/2021, retrospective, USA, North America, preprint, 34 authors, excluded in exclusion analyses: not fully adjusting for the baseline risk differences within systemic autoimmune patients.	**risk of case, 8.5% lower, RR 0.91, *p* = 0.54**, treatment 65 of 1,072 (6.1%), control 200 of 3,594 (5.6%), adjusted per study, odds ratio converted to relative risk.
[Fung], 10/1/2021, retrospective, population-based cohort, USA, North America, preprint, 6 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of death, 15.0% lower, RR 0.85, *p* = 0.10**, vs. past use (better match for systemic autoimmune diseases).
	risk of hospitalization, 5.0% lower, RR 0.95, *p* = 0.41, vs. past use (better match for systemic autoimmune diseases).
	risk of case, 10.0% lower, RR 0.90, *p* = 0.004, vs.

	past use (better match for systemic autoimmune diseases).
	risk of death, 6.0% higher, RR 1.06, *p* = 0.39, vs. never used.
	risk of hospitalization, 4.0% higher, RR 1.04, *p* = 0.32, vs. never used.
	risk of case, 5.0% lower, RR 0.95, *p* = 0.06, vs. never used.
[Gendebien], 6/25/2020, retrospective, Belgium, Europe, preprint, survey, 9 authors, excluded in exclusion analyses: not fully adjusting for the baseline risk differences within systemic autoimmune patients.	risk of case, 3.9% lower, RR 0.96, *p* = 0.93, treatment 12 of 152 (7.9%), control 6 of 73 (8.2%), NNT 308.
[Gendelman], 5/5/2020, retrospective, database analysis, Israel, Middle East, peer-reviewed, 5 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	risk of case, 8.1% lower, RR 0.92, *p* = 0.88, treatment 3 of 36 (8.3%), control 1,314 of 14,484 (9.1%), NNT 135.
[Gentry], 9/21/2020, retrospective, database analysis, USA, North America, peer-reviewed, 6 authors.	risk of death, 91.3% lower, RR 0.09, *p* = 0.10, treatment 0 of 10,703 (0.0%), control 7 of 21,406 (0.0%), NNT 3058, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), COVID-19 mortality within all patients.
	risk of death, 90.7% lower, RR 0.09, *p* = 0.19, treatment 0 of 31 (0.0%), control 7 of 78 (9.0%), NNT 11, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), mortality for infected patients.
	risk of case, 20.9% lower, RR 0.79, *p* = 0.27, treatment 31 of 10,703 (0.3%), control 78 of 21,406 (0.4%), NNT 1338, odds ratio converted to relative risk.
[Gianfrancesco], 5/28/2020, retrospective, database analysis, multiple	risk of hospitalization, 3.3% lower, RR 0.97, *p* = 0.82, treatment 58 of 130 (44.6%), control 219 of

countries, multiple regions, peer-reviewed, 28 authors, excluded in exclusion analyses: not fully adjusting for the baseline risk differences within systemic autoimmune patients.	470 (46.6%), NNT 50, odds ratio converted to relative risk.
[Goenka], 10/24/2020, retrospective, India, South Asia, preprint, 11 authors.	**risk of IgG positive, 87.2% lower, RR 0.13, $p = 0.03$**, treatment 1 of 77 (1.3%), control 115 of 885 (13.0%), NNT 8.6, adjusted per study, odds ratio converted to relative risk.
[Grau-Pujol], 9/21/2020, Randomized Controlled Trial, Spain, Europe, peer-reviewed, 22 authors.	**risk of case, 10.6% lower, RR 0.89, $p = 1.00$**, treatment 1 of 142 (0.7%), control 1 of 127 (0.8%), NNT 1202.
[Gönenli], 12/16/2020, retrospective, Turkey, Europe, preprint, survey, 4 authors.	**risk of pneumonia, 29.7% lower, RR 0.70, $p = 0.77$**, treatment 3 of 148 (2.0%), control 12 of 416 (2.9%), NNT 117.
	risk of case, 18.9% higher, RR 1.19, $p = 0.58$, treatment 8 of 148 (5.4%), control 20 of 416 (4.8%), odds ratio converted to relative risk.
[Huang], 6/16/2020, retrospective, China, Asia, peer-reviewed, 15 authors, excluded in exclusion analyses: significant unadjusted confounding possible.	**risk of hospitalization, 80.0% lower, RR 0.20, $p < 0.001$**, treatment 8, control 1,247.
[Huh], 12/19/2020, retrospective, database analysis, South Korea, Asia, peer-reviewed, 8 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of progression, 251.0% higher, RR 3.51, $p = 0.11$**, treatment 5 of 8 (62.5%), control 873 of 2,797 (31.2%), adjusted per study, multivariate.
	risk of case, 6.0% lower, RR 0.94, $p = 0.82$, treatment 17 of 122 (13.9%), control 7,324 of 43,924 (16.7%), NNT 36, adjusted per study, multivariate.
[Huh (B)], 5/4/2020, retrospective, database analysis, South Korea, Asia, preprint, 10 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of case, 42.6% higher, RR 1.43, $p = 0.09$**, treatment 23 of 274 (8.4%), control 5,149 of 64,875 (7.9%), adjusted per study, odds ratio converted to relative risk, multivariable.
[Jung], 12/11/2020, retrospective, South Korea, Asia, peer-reviewed, 6 authors.	**risk of death, 59.3% lower, RR 0.41, $p = 1.00$**, treatment 0 of 649 (0.0%), control 1 of 1,417 (0.1%), NNT 1417, relative risk is not 0 because of

	continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of case, 13.1% higher, RR 1.13, p = 0.86, treatment 15 of 649 (2.3%), control 31 of 1,417 (2.2%), adjusted per study.
[Kadnur], 7/22/2020, prospective, India, South Asia, preprint, 26 authors.	**risk of case, 86.3% lower, RR 0.14, p = 0.03**, treatment 2 of 248 (0.8%), control 5 of 86 (5.8%), NNT 20, odds ratio converted to relative risk, multivariate logistic regression.
[Kamstrup], 6/1/2021, retrospective, population-based cohort, Denmark, Europe, peer-reviewed, 21 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of hospitalization, 44.0% higher, RR 1.44, p = 0.25**, treatment 5,488, control 54,846, RR approximated with OR.
	risk of case, 10.0% lower, RR 0.90, p = 0.23, treatment 188 of 5,488 (3.4%), control 2,040 of 54,846 (3.7%), NNT 340, adjusted Cox proportional hazards regression.
[Khurana], 7/24/2020, retrospective, India, South Asia, preprint, survey, 5 authors.	**risk of case, 51.0% lower, RR 0.49, p = 0.02**, treatment 6 of 22 (27.3%), control 88 of 159 (55.3%), NNT 3.6, odds ratio converted to relative risk.
[Konig], 5/7/2020, retrospective, database analysis, multiple countries, multiple regions, preprint, 11 authors, excluded in exclusion analyses: not fully adjusting for the baseline risk differences within systemic autoimmune patients.	**risk of hospitalization, 3.0% lower, RR 0.97, p = 0.88**, treatment 16 of 29 (55.2%), control 29 of 51 (56.9%), NNT 59.
[Korkmaz], 6/1/2021, retrospective, Turkey, Europe, preprint, 4 authors.	**risk of death, 82.1% lower, RR 0.18, p = 0.19**, treatment 0 of 385 (0.0%), control 2 of 299 (0.7%), NNT 150, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of case, 93.7% lower, RR 0.06, p < 0.001, treatment 2 of 395 (0.5%), control 24 of 299 (8.0%), NNT 13.
[Küçükakkaş], 7/20/2021, retrospective, Turkey, Europe, preprint, 2 authors, excluded in exclusion analyses: minimal details of groups provided.	**risk of ICU admission, 42.9% higher, RR 1.43, p = 1.00**, treatment 1 of 7 (14.3%), control 1 of 10 (10.0%).

[Laplana], 9/9/2020, retrospective, Spain, Europe, peer-reviewed, survey, 3 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of case, 56.0% higher, RR 1.56, p = 0.24**, treatment 17 of 319 (5.3%), control 11 of 319 (3.4%).
[Macias], 5/16/2020, retrospective, database analysis, Spain, Europe, preprint, 12 authors, excluded in exclusion analyses: not fully adjusting for the baseline risk differences within systemic autoimmune patients.	**risk of hospitalization, 25.5% lower, RR 0.74, p = 1.00**, treatment 1 of 290 (0.3%), control 2 of 432 (0.5%), NNT 846.
	risk of case, 49.0% higher, RR 1.49, p = 0.53, treatment 5 of 290 (1.7%), control 5 of 432 (1.2%).
[Mathai], 11/6/2020, retrospective, India, South Asia, peer-reviewed, 3 authors.	**risk of case, 89.5% lower, RR 0.10, p < 0.001**, treatment 10 of 491 (2.0%), control 22 of 113 (19.5%), NNT 5.7.
	risk of case, 88.5% lower, RR 0.12, p < 0.001, treatment 5 of 491 (1.0%), control 10 of 113 (8.8%), NNT 13, symptomatic.
[McKinnon], 12/23/2021, Double Blind Randomized Controlled Trial, USA, North America, peer-reviewed, 10 authors.	**risk of symptomatic case, 2.5% lower, RR 0.98, p = 1.00**, treatment 2 of 365 (0.5%), control 1 of 178 (0.6%), NNT 7219, daily and weekly HCQ combined.
	risk of symptomatic case, no change, RR 1.00, p = 1.00, treatment 1 of 178 (0.6%), control 1 of 178 (0.6%), daily HCQ.
	risk of symptomatic case, 4.8% lower, RR 0.95, p = 1.00, treatment 1 of 187 (0.5%), control 1 of 178 (0.6%), NNT 3698, weekly HCQ.
	risk of symptomatic case, 53.3% lower, RR 0.47, p = 1.00, treatment 0 of 25 (0.0%), control 1 of 178 (0.6%), NNT 178, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), AD patients.
	risk of case, 51.2% lower, RR 0.49, p = 0.60, treatment 2 of 365 (0.5%), control 2 of 178 (1.1%), NNT 174, daily and weekly HCQ combined.
	risk of case, 50.0% lower, RR 0.50, p = 1.00, treatment 1 of 178 (0.6%), control 2 of 178 (1.1%), NNT 178, daily HCQ.

	risk of case, 52.4% lower, RR 0.48, p = 0.61, treatment 1 of 187 (0.5%), control 2 of 178 (1.1%), NNT 170, weekly HCQ.
	risk of case, 69.5% lower, RR 0.30, p = 1.00, treatment 0 of 25 (0.0%), control 2 of 178 (1.1%), NNT 89, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), AD patients.
[Mitchell], 5/5/2020, retrospective, multiple countries, multiple regions, preprint, 2 authors, excluded in exclusion analyses: excessive unadjusted differences between groups.	**risk of death, 99.0% lower, RR 0.01, p < 0.001**.
[Naggie], 8/25/2021, Randomized Controlled Trial, USA, North America, preprint, 22 authors.	**risk of symptomatic case, 23.5% lower, RR 0.76, p = 0.18**, treatment 41 of 683 (6.0%), control 53 of 676 (7.8%), NNT 54, odds ratio converted to relative risk, logistic regression.
	risk of symptomatic case, 29.3% lower, RR 0.71, p = 0.18, treatment 41 of 683 (6.0%), control 53 of 676 (7.8%), NNT 54, odds ratio converted to relative risk, Mantel–Haenszel.
[Patil], 8/24/2021, prospective, India, South Asia, preprint, 20 authors.	**risk of death, 65.9% lower, RR 0.34, p = 0.10**, treatment 5,266, control 3,946.
	risk of case, 9.1% lower, RR 0.91, p = 0.43, treatment 167 of 5,266 (3.2%), control 147 of 3,946 (3.7%), NNT 181, adjusted per study.
[Pham], 3/2/2021, retrospective, USA, North America, peer-reviewed, 5 authors.	**risk of death, 19.7% lower, RR 0.80, p = 0.77**, treatment 2 of 14 (14.3%), control 5 of 28 (17.9%), NNT 28, odds ratio converted to relative risk, univariate.
	risk of ICU admission, 35.5% higher, RR 1.35, p = 0.61, treatment 4 of 14 (28.6%), control 6 of 28 (21.4%), odds ratio converted to relative risk, univariate.
[Rajasingham], 9/21/2020, Randomized Controlled Trial, USA, North America, peer-reviewed, 22 authors.	**risk of hospitalization, 50.1% lower, RR 0.50, p = 1.00**, treatment 1 of 989 (0.1%), control 1 of 494 (0.2%), NNT 987.

	risk of case, 27.0% lower, RR 0.73, p = 0.12, treatment 58 of 989 (5.9%), control 39 of 494 (7.9%), NNT 49.
[Rangel], 1/10/2021, retrospective, USA, North America, peer-reviewed, 5 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of death, 25.1% lower, RR 0.75, p = 0.77**, treatment 4 of 50 (8.0%), control 11 of 103 (10.7%), NNT 37, from all patients.
	risk of hospitalization, 22.2% lower, RR 0.78, p = 0.29, treatment 17 of 50 (34.0%), control 45 of 103 (43.7%), NNT 10.
	hospitalization time, 41.2% lower, relative time 0.59, p = 0.12, treatment 21, control 54.
[Rao], 12/4/2021, prospective, India, South Asia, peer-reviewed, 8 authors, excluded in exclusion analyses: unadjusted results with minimal group details.	**risk of case, 11.0% lower, RR 0.89, p = 0.68**, treatment 16 of 273 (5.9%), control 67 of 1,021 (6.6%), NNT 143.
[Rentsch], 9/9/2020, retrospective, population-based cohort, database analysis, United Kingdom, Europe, peer-reviewed, 34 authors, excluded in exclusion analyses: not fully adjusting for the baseline risk differences within systemic autoimmune patients, medication adherence unknown and may significantly change results.	**risk of death, 3.0% higher, RR 1.03, p = 0.83**, treatment 70 of 30,569 (0.2%), control 477 of 164,068 (0.3%), NNT 1620, adjusted per study.
[Revollo], 11/21/2020, retrospective, propensity score matching, Spain, Europe, peer-reviewed, 16 authors.	**risk of case, 23.0% lower, RR 0.77, p = 0.52**, treatment 16 of 69 (23.2%), control 65 of 418 (15.6%), adjusted per study, PSM, risk of PCR+.
	risk of case, 43.0% higher, RR 1.43, p = 0.42, treatment 17 of 60 (28.3%), control 62 of 404 (15.3%), adjusted per study, PSM, risk of IgG+.
[Rojas-Serrano], 5/16/2021, Double Blind Randomized Controlled Trial, Mexico, North America, preprint, 8 authors.	**risk of symptomatic case, 82.0% lower, RR 0.18, p = 0.12**, treatment 1 of 62 (1.6%), control 6 of 65 (9.2%), NNT 13, adjusted per study.
[Salvarani], 8/6/2020, retrospective, population-based cohort, Italy, Europe, peer-reviewed, 18 authors, excluded in	**risk of case, 6.0% lower, RR 0.94, p = 0.75**, RR approximated with OR.

exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	
[Samajdar], 11/17/2021, retrospective, India, South Asia, peer-reviewed, 9 authors, 1 September, 2020 - 31 December, 2020, dosage not specified, excluded in exclusion analyses: minimal details provided, unadjusted results with no group details, results may be significantly affected by survey bias.	**risk of case, 74.5% lower, RR 0.25, $p < 0.001$**, treatment 12 of 129 (9.3%), control 29 of 81 (35.8%), NNT 3.8, odds ratio converted to relative risk, physician survey.
	risk of case, 48.6% lower, RR 0.51, $p = 0.03$, treatment 11 of 109 (10.1%), control 39 of 200 (19.5%), NNT 11, odds ratio converted to relative risk, combined ivermectin or HCQ in community.
[Singer], 8/5/2020, retrospective, database analysis, USA, North America, preprint, 3 authors, excluded in exclusion analyses: not fully adjusting for the baseline risk differences within systemic autoimmune patients.	**risk of case, 9.0% higher, RR 1.09, $p = 0.62$**, treatment 55 of 10,700 (0.5%), control 104 of 22,058 (0.5%).
[Syed], 5/17/2021, Randomized Controlled Trial, Pakistan, South Asia, peer-reviewed, 8 authors.	**risk of symptomatic case, 59.7% higher, RR 1.60, $p = 0.41$**, treatment 10 of 48 (20.8%), control 6 of 46 (13.0%), group 1.
	risk of symptomatic case, 110.5% higher, RR 2.10, $p = 0.13$, treatment 14 of 51 (27.5%), control 6 of 46 (13.0%), group 2.
	risk of symptomatic case, 16.4% lower, RR 0.84, $p = 0.77$, treatment 6 of 55 (10.9%), control 6 of 46 (13.0%), NNT 47, group 3.
	risk of case, 91.7% higher, RR 1.92, $p = 0.12$, treatment 15 of 38 (39.5%), control 7 of 34 (20.6%), group 1.
	risk of case, 136.6% higher, RR 2.37, $p = 0.02$, treatment 19 of 39 (48.7%), control 7 of 34 (20.6%), group 2.
	risk of case, 21.4% higher, RR 1.21, $p = 0.77$, treatment 8 of 32 (25.0%), control 7 of 34 (20.6%), group 3.
[Trefond], 1/27/2021, retrospective, France, Europe, peer-reviewed, 21	**risk of death, 16.6% higher, RR 1.17, $p = 0.80$**, treatment 4 of 68 (5.9%), control 12 of 183 (6.6%),

authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients, significant unadjusted confounding possible, excessive unadjusted differences between groups.	NNT 148, adjusted per study, odds ratio converted to relative risk.
	risk of death/ICU, 78.2% higher, RR 1.78, *p* = 0.21, treatment 8 of 71 (11.3%), control 18 of 191 (9.4%), adjusted per study, odds ratio converted to relative risk.
	risk of hospitalization, 44.9% higher, RR 1.45, *p* = 0.12, treatment 24 of 71 (33.8%), control 53 of 191 (27.7%), adjusted per study, odds ratio converted to relative risk.
[Vivanco-Hidalgo], 3/9/2021, retrospective, Spain, Europe, peer-reviewed, 8 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	**risk of hospitalization, 46.0% higher, RR 1.46, *p* = 0.10**, treatment 40 of 6,746 (0.6%), control 50 of 13,492 (0.4%), adjusted per study.
	risk of case, 8.0% higher, RR 1.08, *p* = 0.50, treatment 97 of 6,746 (1.4%), control 183 of 13,492 (1.4%), adjusted per study.
[Yadav], 9/30/2020, retrospective, India, South Asia, preprint, 11 authors.	**risk of hospitalization, 82.4% lower, RR 0.18, *p* = 0.01**, treatment 2 of 279 (0.7%), control 9 of 221 (4.1%), NNT 30, PCR+.
	risk of IgG+, 41.8% lower, RR 0.58, *p* = 0.049, treatment 17 of 178 (9.6%), control 27 of 221 (12.2%), NNT 38, odds ratio converted to relative risk, multivariate logistic regression.
	risk of IgG+, 79.0% lower, RR 0.21, *p* = 0.09, treatment 1 of 39 (2.6%), control 27 of 221 (12.2%), NNT 10, HCQ >10 weeks.
	risk of IgG+, 52.4% lower, RR 0.48, *p* = 0.14, treatment 5 of 86 (5.8%), control 27 of 221 (12.2%), NNT 16, HCQ 6-10 weeks.
	risk of IgG+, 69.9% higher, RR 1.70, *p* = 0.12, treatment 11 of 53 (20.8%), control 27 of 221 (12.2%), HCQ <6 weeks.
[Zhong (B)], 7/3/2020, retrospective, database analysis, China, Asia, peer-reviewed, 20 authors.	**risk of case, 91.0% lower, RR 0.09, *p* = 0.04**, treatment 7 of 16 (43.8%), control 20 of 27 (74.1%), NNT 3.3, adjusted per study.

Post-Exposure Prophylaxis

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. Only the first (most serious) outcome is used in pooled analysis, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

[Barnabas], 12/7/2020, Randomized Controlled Trial, USA, North America, peer-reviewed, 30 authors.	risk of hospitalization, 3.7% higher, RR 1.04, p = 1.00, treatment 1 of 407 (0.2%), control 1 of 422 (0.2%).
	risk of case, 27.0% higher, RR 1.27, p = 0.33, treatment 43 of 353 (12.2%), control 33 of 336 (9.8%), adjusted per study, day 14 symptomatic mITT PCR+ AIM.
	risk of case, 23.0% higher, RR 1.23, p = 0.41, treatment 40 of 317 (12.6%), control 32 of 309 (10.4%), adjusted per study, day 14 symptomatic mITT PCR+ IDWeek.
	risk of case, 10.0% higher, RR 1.10, p = 0.66, treatment 53 of 353 (15.0%), control 45 of 336 (13.4%), adjusted per study, day 14 PCR+ mITT AIM.
	risk of case, 1.0% lower, RR 0.99, p = 0.97, treatment 46 of 317 (14.5%), control 43 of 309 (13.9%), adjusted per study, day 14 PCR+ mITT IDWeek.
	risk of case, 19.0% lower, RR 0.81, p = 0.23, treatment 82 of 387 (21.2%), control 99 of 393 (25.2%), NNT 25, adjusted per study, day 14 PCR+ ITT AIM.
[Boulware (B)], 6/3/2020, Randomized Controlled Trial, USA, North America, peer-reviewed, 24 authors.	risk of case, 17.0% lower, RR 0.83, p = 0.35, treatment 49 of 414 (11.8%), control 58 of 407 (14.3%), NNT 41.
	risk of case, 25.1% lower, RR 0.75, p = 0.22, treatment 32 of 414 (7.7%), control 42 of 407 (10.3%), NNT 39, probable COVID-19 cases.
[Dhibar], 11/6/2020, prospective, India, South Asia, peer-reviewed, 13 authors.	risk of case, 41.0% lower, RR 0.59, p = 0.03, treatment 14 of 132 (10.6%), control 36 of 185 (19.5%), NNT 11, adjusted per study.

	risk of case, 50.0% lower, RR 0.50, *p* = 0.04, treatment 10 of 132 (7.6%), control 28 of 185 (15.1%), NNT 13, adjusted per study, PCR+.
	risk of symptomatic case, 43.9% lower, RR 0.56, *p* = 0.21, treatment 6 of 132 (4.5%), control 15 of 185 (8.1%), NNT 28, adjusted per study.
[Mitjà (B)], 7/26/2020, Randomized Controlled Trial, Spain, Europe, peer-reviewed, 12 authors.	**risk of death, 51.7% lower, RR 0.48, *p* = 0.27**, treatment 4 of 1,196 (0.3%), control 9 of 1,301 (0.7%), NNT 280, per supplemental appendix table S7, one treatment death was a patient that did not take any study medication, they have been moved to the control group.
	risk of hospitalization, 21.4% lower, RR 0.79, *p* = 0.59, treatment 13 of 1,196 (1.1%), control 18 of 1,301 (1.4%), NNT 337, per supplemental appendix table S7, one treatment death was a patient that did not take any study medication, they have been moved to the control group.
	baseline pcr- risk of cases, 32.0% lower, RR 0.68, *p* = 0.27, treatment 29 of 958 (3.0%), control 45 of 1,042 (4.3%), NNT 77.
[Polat], 9/30/2020, prospective, Turkey, Europe, peer-reviewed, 3 authors.	**risk of case, 57.0% lower, RR 0.43, *p* = 0.03**, treatment 12 of 138 (8.7%), control 14 of 70 (20.0%), NNT 8.8.
[Seet], 4/14/2021, Cluster Randomized Controlled Trial, Singapore, Asia, peer-reviewed, 15 authors, dosage 400mg day 1, 200mg days 2-42, this trial compares with another treatment - results may be better when compared to placebo.	**risk of symptomatic case, 35.1% lower, RR 0.65, *p* = 0.047**, treatment 29 of 432 (6.7%), control 64 of 619 (10.3%), NNT 28.
	risk of case, 32.0% lower, RR 0.68, *p* = 0.009, treatment 212 of 432 (49.1%), control 433 of 619 (70.0%), NNT 4.8, adjusted per study, odds ratio converted to relative risk, model 6.
[Shabani], 8/10/2021, prospective, Iran, Middle East, peer-reviewed, 16 authors.	**risk of symptomatic case, 19.0% lower, RR 0.81, *p* = 1.00**, treatment 2 of 51 (3.9%), control 3 of 62 (4.8%), NNT 109, day 7.
	risk of case, 6.4% higher, RR 1.06, *p* = 1.00, treatment 7 of 51 (13.7%), control 8 of 62 (12.9%), day 7, PCR+ and symptomatic.

	risk of case, 21.6% higher, RR 1.22, *p* = 0.78, treatment 7 of 51 (13.7%), control 7 of 62 (11.3%), day 7, PCR+ only.
[Simova (B)], 11/12/2020, retrospective, Bulgaria, Europe, peer-reviewed, 5 authors.	risk of case, 92.7% lower, RR 0.07, *p* = 0.01, treatment 0 of 156 (0.0%), control 3 of 48 (6.2%), NNT 16, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).

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