

Targeted Update: Safety and efficacy of hydroxychloroquine or chloroquine for treatment of COVID-19

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Informed decisions.
Better health.**

Search date: 11th June 2020

Included studies

This targeted update includes data from three randomised controlled trials and two quasi-experimental studies comparing the use of hydroxychloroquine or chloroquine with standard care as a treatment for COVID-19.

Key findings

Very low certainty evidence suggested that hydroxychloroquine used in the treatment of COVID-19:

- May result in little or no difference in all-cause mortality at day 7 compared with standard care
- May result in little or no difference in viral negative conversion at day 7 compared with standard care
- May result in an increased risk of adverse events during days 14-28 compared to standard care
- May result in little or no difference in serious adverse events at day 7 compared with standard care

Main conclusions

The current evidence on the efficacy and safety of hydroxychloroquine for the treatment of COVID-19 is limited and of very low certainty. Hydroxychloroquine was not associated with a difference in overall mortality when compared to standard care for the treatment of COVID-19. Limited evidence suggested that hydroxychloroquine may result in more adverse events than standard care for treatment of COVID-19.

The overall certainty of the evidence for all outcomes was very low, therefore these results need to be interpreted with caution.

Summary

Background

In December 2019, a novel coronavirus outbreak was documented in Wuhan, Hubei Province, China. Over the first six weeks of the new decade, this novel coronavirus, known as SARS-CoV-2, had spread from China to 20 other countries and on March 11, 2020 the World Health Organization (WHO) declared a pandemic. To overcome this pandemic, researchers are actively working to accelerate the development of diagnostics, preventive interventions, therapeutics, and vaccines.

This emerging situation requires an optimum planning and conduct of research as well as strategies for the appropriate transposition of research into practice. Therefore, decision-makers and researchers urgently need a complete, high-quality, and up-to-date synthesis of data from all ongoing research studies as soon as they are available.

To this end, the following work is being conducted: 1) a living mapping of registered randomised controlled trials (RCTs) and 2) a living systematic review and network meta-analysis of RCTs and quasi-experimental studies.

Objective

The objective of this targeted update is to review the safety and efficacy of hydroxychloroquine or chloroquine for treatment of COVID-19.

Methods

The protocol and data for this targeted update comes from the COVID-NMA project led by Cochrane France in collaboration with Cochrane Germany, Cochrane Ireland, the Centre for Evidence-Based Medicine Odense, the Centre of Research Epidemiology and Statistics (Université de Paris, Inserm). This project receives some funding from the ANR (Agence Nationale de la Recherche, France).

Search methods

The WHO International Clinical Trials Registry Platform and electronic bibliographic databases (PubMed, MedRxiv, Chinaxiv) are searched weekly. Systematic review and meta-analyses of COVID-19 treatments are being retrieved and the references screened. No language restrictions are used.

The most recent search was conducted on June 11, 2020.

Selection criteria

RCTs and quasi-experimental studies are eligible for inclusion. Early-phase clinical trials, single arm trials, observational studies, and modelling studies of interventions for COVID-19 are also identified but are not formally included in the review.

Studies including patients with suspected, probable, or confirmed COVID-19, evaluating effectiveness of interventions for treating COVID-19, are considered for inclusion. The efficacy of these treatments is evaluated according to the severity of the disease (i.e., mild, moderate, severe, and critical).

The focus of this targeted update is on the efficacy and safety of hydroxychloroquine or chloroquine, compared to standard care for treatment of COVID-19.

The outcome selection is based on the core outcome sets (COS) developed by the WHO and on the meta-COS for research in COVID-19 hospitalised patients identified through the COMET initiative (www.comet-initiative.org/Studies/Details/1538). We consider viral negative conversion, clinical improvement, the WHO Clinical Progression Score level 5 or above; 6 or above; 7 or above; adverse events; serious adverse events; and all-cause mortality.

For this targeted update we have also evaluated adverse events that have been associated with hydroxychloroquine and chloroquine (i.e. QT interval prolongation, arrhythmia, and ventricular fibrillation resulting in sudden death).

Data collection and analysis

Screening, data extraction and risk of bias assessment was performed in duplicate by two independent reviewers.

The risk of bias assessment was conducted using the Cochrane Risk of Bias tool—version 2 (RoB 2) (Sterne 2019) and the ROBINS-I tool for observational studies (Sterne 2016).

For dichotomous outcomes from RCTs, risk ratios (RR) or hazard ratios (HR) with 95% confidence intervals (CI) were calculated for each study and pooled using a random effects model (DerSimonian & Laird 1986).

Findings were interpreted using the GRADE approach (Schünemann 2019). See Appendix 1 for details.

See full published protocol (Boutron 2020) for additional details and the website for full details of included studies (www.covid-nma.com).

Main Results

The comparisons reported here focus on data from RCTs and quasi-experimental studies. In addition, Appendix 2 lists the details and results of observational studies and case series that reported on hydroxychloroquine or chloroquine as a treatment for COVID-19.

Comparison 1. Hydroxychloroquine compared with Standard Care for moderate and severe COVID-19

See Summary of Findings table 1 and Forest plots 1.

Three RCTs (J Chen 2020, Z Chen 2020, Tang 2020) and two quasi-experimental studies (Geleris 2020, Mahevas 2020) were included in this comparison. Three studies were carried out in China, one in France and one in the USA.

Four studies included patients with moderate or severe COVID-19 (Mahevas 2020, J Chen 2020, Z Chen 2020, Tang 2020). One study did not report information on severity of the disease (Geleris 2020).

Mortality

Two RCTs reported on all-cause mortality. We do not know about the effect of hydroxychloroquine on all-cause mortality because there were no deaths reported at 7 days (1 RCT, N=150) or at 14-28 days (2 RCTs, N=180) and the certainty of the evidence was very low.

In addition, one quasi-experimental study reported on all-cause mortality and time to death. The study reported little or no difference in all-cause mortality at

7 days between the hydroxychloroquine group and those receiving standard care (RR 0.93, 95% CI 0.48 to 1.81, N=173) but this evidence was of very low certainty. The same study also reported little or no difference in time to death between both groups (HR 1.20, 95% CI 0.42 to 3.45, N=173) and this evidence was also of very low certainty.

We do not know about the effect of hydroxychloroquine compared to standard care on the time to intubation/mechanical ventilation or death (HR 0.98, 95% CI 0.73 to 1.31, N=1085, 1 quasi-experimental study), incidence of viral negative conversion at day 7 (RR 0.93, 95% CI 0.73 to 1.18, N=30, 1 RCT), or time to 2019-nCoV RT-PCR negativity (HR 0.85, 95% CI 0.58 to 1.23, N=150, 1 RCT) because the certainty of evidence for these outcomes was very low.

Safety

The evidence for all of the safety outcomes was of very low certainty because there were some concerns due to risk of bias in the included studies, the studies included only a small number of participants, and very few adverse events were reported.

In one RCT with 62 participants, 2/31 people in the intervention group and 0/31 in the control group experienced adverse events at day 7 (RR 5.00, 95% CI 0.25 to 100.08). No serious adverse events were reported in either group at day 7.

Pooled results from two RCTs showed an effect estimate in favour of standard care for adverse events at 14-28 days compared to hydroxychloroquine (RR 2.49, 95% CI 1.04 to 5.98, N=180). Of the two RCTs, one reported more adverse events with hydroxychloroquine while the other reported no

differences between groups. Little or no difference was seen in serious adverse events at 14-28 days, with 2/70 participants in the intervention group and 0/80 in the control group experiencing serious adverse events (RR 5.70, 95% CI 0.28 to 116.84, 1 RCT, N=150).

One RCT reported no cases of QT interval prolongation or cardiac arrhythmia resulting in sudden death in the group of patients receiving hydroxychloroquine (N=150, very low certainty evidence).

Implications and conclusions

This targeted update reports on all available evidence for the treatment of COVID-19 with hydroxychloroquine or chloroquine compared to standard care and is current to 11th June 2020.

No RCTs or quasi-experimental studies were identified that compared chloroquine to standard care for the treatment of COVID-19.

There is very low certainty evidence from RCTs and quasi-experimental studies that hydroxychloroquine results in little or no benefit over standard care for the treatment of COVID-19.

There is also very low certainty evidence of little to no difference in overall mortality between hydroxychloroquine and standard care.

With regards to safety outcomes, there is very low certainty evidence that hydroxychloroquine results in more adverse events than standard care at day 14-28. The clinical relevance of this finding is unclear. Evidence for other safety outcomes such as serious adverse events, cardiac arrhythmia, and QT interval prolongation resulting in sudden death was limited and of very low certainty.

Summary of Findings 1: Hydroxychloroquine compared to Standard Care for Moderate/Severe COVID-19

Patients: Moderate/Severe COVID-19

Setting: China, USA, and France

Comparison: Hydroxychloroquine vs Standard Care

Study design: randomised controlled trials (RCTs) and quasi-experimental studies

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants & studies	Certainty of the evidence (GRADE)	Comments
	Risk with Standard Care	Risk with Hydroxychloroquine				
All-cause mortality D7	-	-	-	150 (1 RCT)	⊕○○○ VERY LOW ^{a,b,c}	zero events in both groups
	-	-	RR 0.93 (0.48 to 1.81)	173 (1 quasi-experimental study)	⊕○○○ VERY LOW ^{b,d,e}	moderate/severe cases
All-cause mortality D14-D28	-	-	-	180 (2 RCTs)	⊕○○○ VERY LOW ^{a,c,f}	zero events in both groups
Time to death	-	-	HR 1.20 (0.42 to 3.45)	173 (1 quasi-experimental study)	⊕○○○ VERY LOW ^{b,d,e}	moderate/severe cases
Time to intubation/mechanical ventilation or death	-	-	HR 0.98 (0.73 to 1.31)	1085 (1 quasi-experimental study)	⊕○○○ VERY LOW ^{d,g}	severity not reported
Incidence of viral negative conversion D7	933 per 1.000	868 per 1.000 (681 to 1.000)	RR 0.93 (0.73 to 1.18)	30 (1 RCT)	⊕○○○ VERY LOW ^{d,h,i}	moderate/severe cases
Time to 2019-nCoV RT-PCR negativity	-	-	HR 0.85 (0.58 to 1.23)	150 (1 RCT)	⊕○○○ VERY LOW ^{a,b,d}	moderate/severe cases
WHO Clinical Progression Score (decrease in 1 point) (i.e., improvement)	-	-	-	-	-	outcome not yet measured or reported
Admission in ICU or death	-	-	-	-	-	outcome not yet measured or reported
Incidence of WHO progression score (level 6 or above)	-	-	-	-	-	outcome not yet measured or reported
Incidence of WHO progression score (level 7 or above)	-	-	-	-	-	outcome not yet measured or reported
Adverse events D7	0 per 1.000	65 per 1.000**	RR 5.00 (0.25 to 100.08)	62 (1 RCT)	⊕○○○ VERY LOW ^{j,k,l}	zero events in control group

Adverse events D14-D28	105 per 1.000	262 per 1.000 (109 to 629)	RR 2.49 (1.04 to 5.98)	180 (2 RCTs)	⊕○○○ VERY LOW _{a,k,m}	
Serious adverse events D7	-	-	-	62 (1 RCT)	⊕○○○ VERY LOW _{c,j,k}	zero events in both groups
Serious adverse events D14-D28	0 per 1.000	29 per 1.000**	RR 5.70 (0.28 to 116.84)	150 (1 RCT)	⊕○○○ VERY LOW _{a,k,l}	zero events in control group
QT interval prolongation	One RCT (Tang 2020) reported no cases of QT interval prolongation (0/150) in the intervention group. Data not reported for standard care group.				⊕○○○ VERY LOW ⁿ	moderate/severe cases
Cardiac arrhythmia	One RCT (Tang 2020) reported no cases of cardiac arrhythmia (0/150) in the intervention group. Data not reported for standard care group.				⊕○○○ VERY LOW _{a,b,c}	moderate/severe cases
Ventricular fibrillation sudden death	-	-	-	-	-	outcome not yet measured or reported

CI=confidence interval, RR=risk ratio

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

****Where there are no events in the control group**, the risk in the intervention group is based on the absolute risk reported in the studies.

Explanations

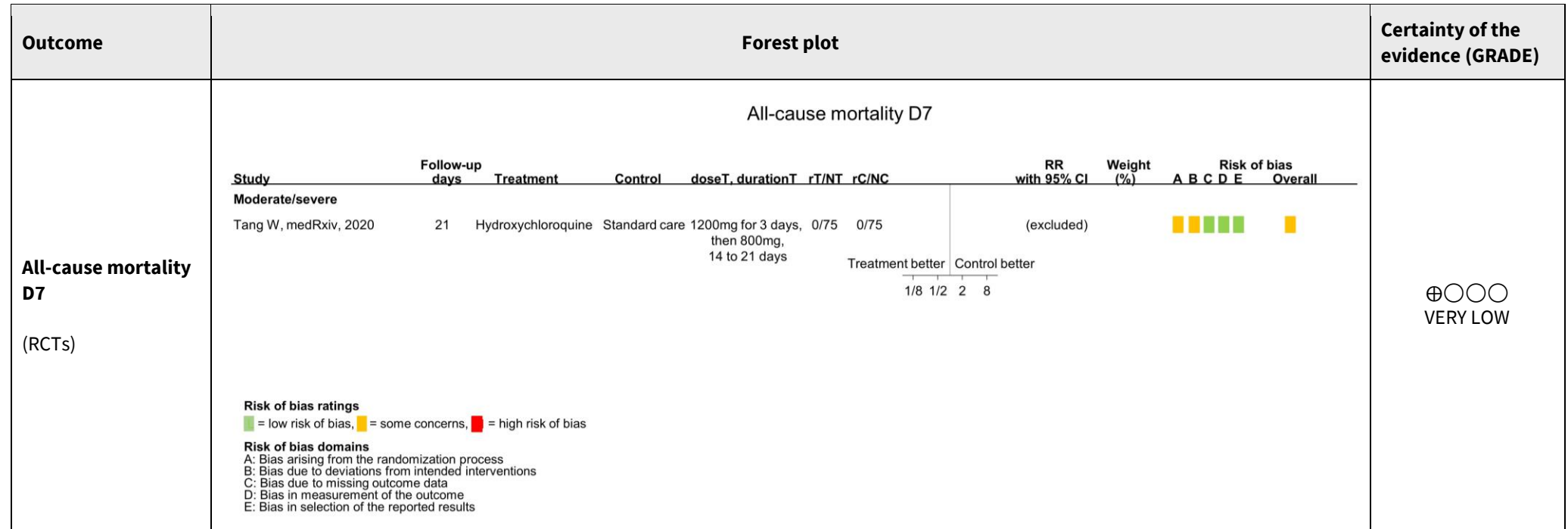
- a. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviations from intended interventions and selection of the reported results
- b. Indirectness downgraded by 1 level: single study from a single country, therefore results in this population might not be generalizable to other settings
- c. Imprecision downgraded by 2 levels: no events in both groups and low number of participants
- d. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and very low number of participants
- e. Risk of bias downgraded by 1 level: moderate risk of bias due to confounding, selection of participants into study, and selection of the reported result. No information about deviations from intended interventions.
- f. Indirectness downgraded by 1 level: studies from a single country, therefore results in this population might not be generalizable to other settings
- g. Risk of bias downgraded by 2 levels: moderate risk of bias due to confounding and selection of the reported result; serious risk of bias due to selection of participants. No information about deviations from intended interventions.
- h. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization and selection of the reported results
- i. Indirectness downgraded by 1 level: single study from a single institution, therefore results in this population might not be generalizable to other settings
- j. Risk of bias downgraded by 1 level: high risk of bias and some concerns regarding adequate randomization, deviations from intended interventions and selection of the reported results
- k. We presume that the adverse event rates, and the corresponding relative risks, are similar across diverse settings; therefore, not downgraded for indirectness
- l. Imprecision downgraded by 2 levels: due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
- m. Imprecision downgraded by 2 levels: due to wide confidence interval consistent with a benefit of unknown clinical relevance and a low number of participants
- n. Only non-comparative estimates (i.e. no control group) reported which are of very low certainty.

Forest plots 1: Hydroxychloroquine versus Standard Care for Moderate/Severe COVID-19

Patients: Moderate/Severe COVID-19

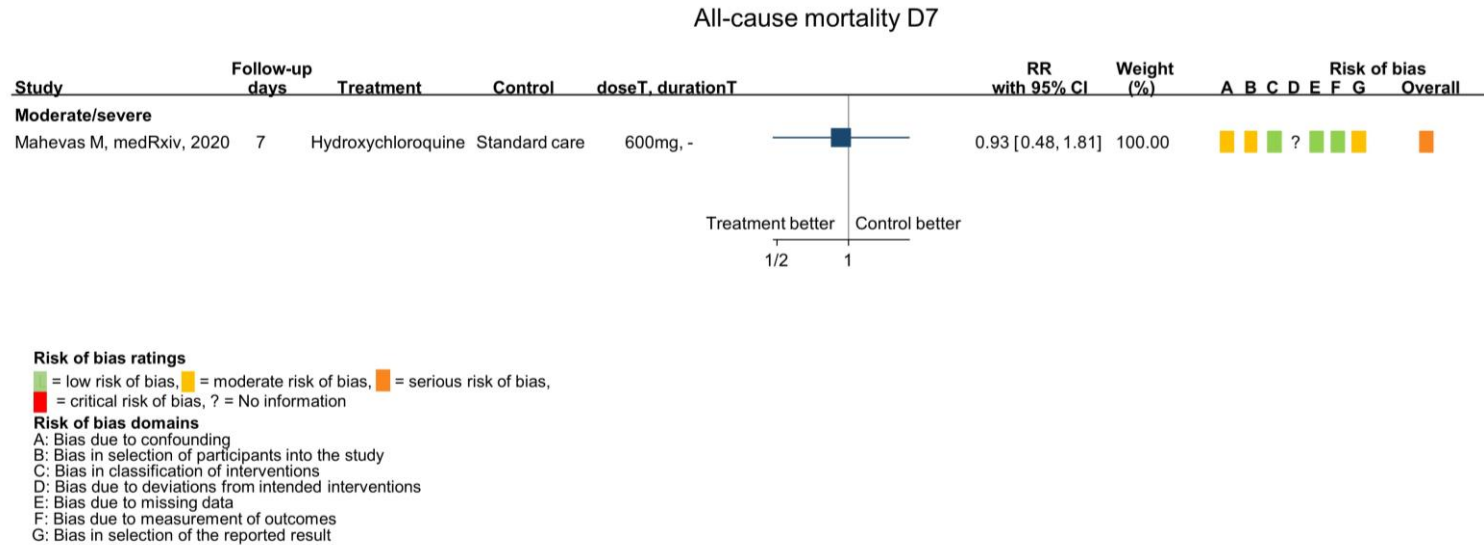
Setting: China, USA, and France

Comparison: Hydroxychloroquine vs Standard Care



All-cause mortality D7

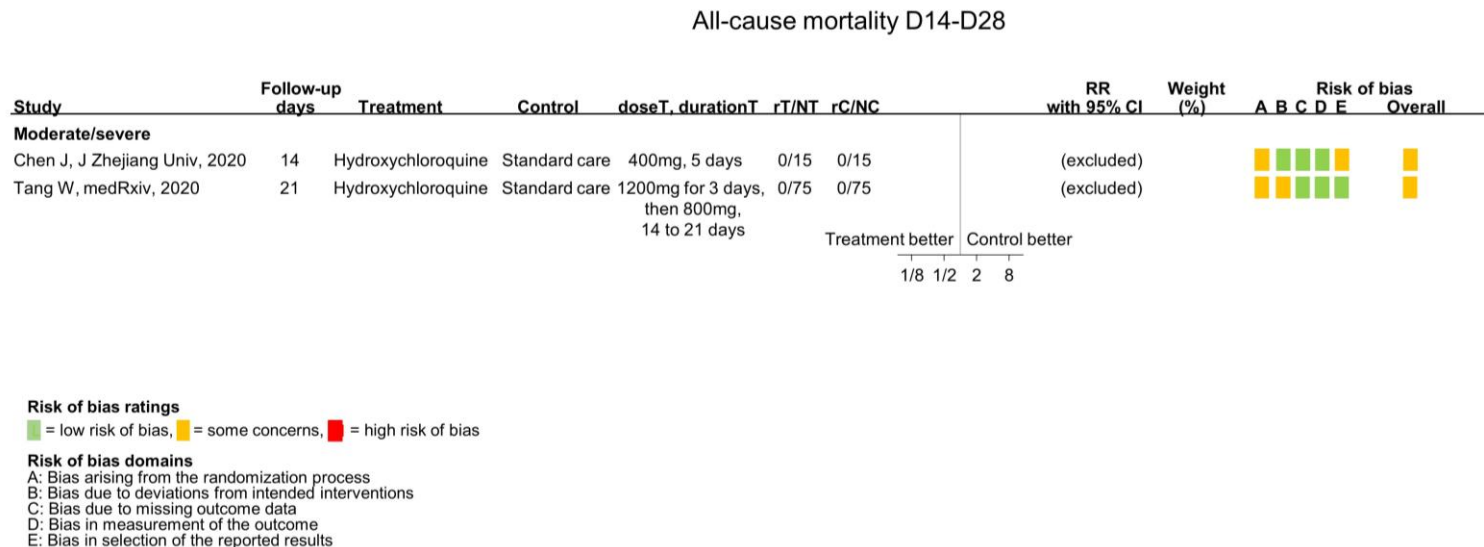
(quasi-experimental study)



⊕○○○
VERY LOW

All-cause mortality D14-D28

(RCTs)



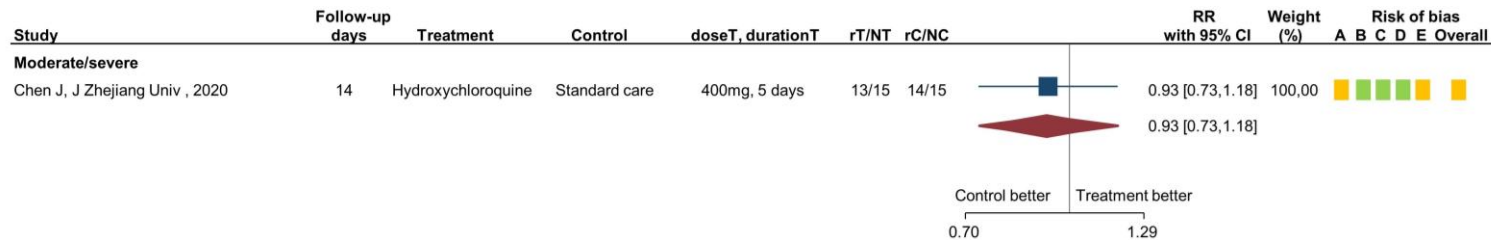
⊕○○○
VERY LOW

<div>Time to death</div> <div>(quasi-experimental studies)</div>	<div>Time to death</div> <table><thead><tr><th>Study</th><th>Follow-up days</th><th>Treatment</th><th>Control</th><th>doseT</th><th></th><th>HR with 95% CI</th><th>Weight (%)</th><th colspan="7">Risk of bias</th></tr><tr><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th>A</th><th>B</th><th>C</th><th>D</th><th>E</th><th>F</th><th>G</th><th>Overall</th></tr></thead><tbody><tr><td colspan="16">Moderate/severe</td></tr><tr><td>Mahevas M, Bmj, 2020</td><td>21</td><td>Hydroxychloroquine</td><td>Standard care</td><td>600mg,</td><td></td><td>1.20 [0.42, 3.45]</td><td>100.00</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr></tbody></table> <div><div>Risk of bias ratings</div><div> = low risk of bias, = moderate risk of bias, = serious risk of bias, = critical risk of bias, ? = No information</div><div>Risk of bias domains</div><div>A: Bias due to confounding B: Bias in selection of participants into the study C: Bias in classification of interventions D: Bias due to deviations from intended interventions E: Bias due to missing data F: Bias due to measurement of outcomes G: Bias in selection of the reported result</div></div>	Study	Follow-up days	Treatment	Control	doseT		HR with 95% CI	Weight (%)	Risk of bias															A	B	C	D	E	F	G	Overall	Moderate/severe																Mahevas M, Bmj, 2020	21	Hydroxychloroquine	Standard care	600mg,		1.20 [0.42, 3.45]	100.00									<div>⊕○○○</div> <div>VERY LOW</div>
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Incidence of viral negative conversion D7

(RCTs)

Incidence of viral negative conversion D7



Risk of bias ratings

■ = low risk of bias, ■ = some concerns, ■ = high risk of bias

Risk of bias domains

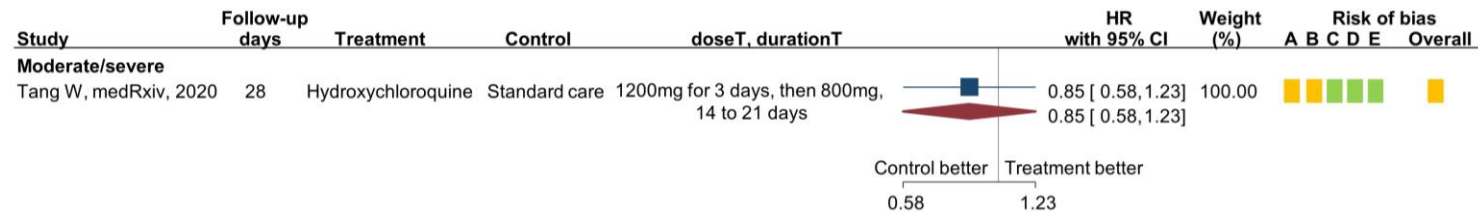
A: Bias arising from the randomization process
 B: Bias due to deviations from intended interventions
 C: Bias due to missing outcome data
 D: Bias in measurement of the outcome
 E: Bias in selection of the reported results

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VERY LOW

Time to 2019-nCoV RT-PCR negativity

(RCTs)

Time to 2019-nCoV RT-PCR negativity



Risk of bias ratings

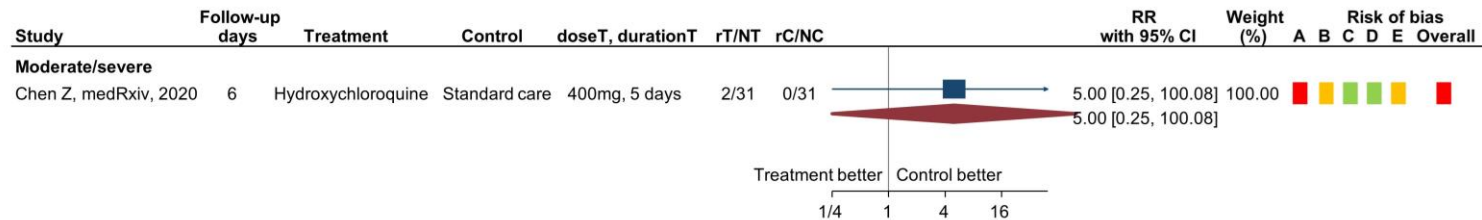
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VERY LOW

Adverse events D7

**Risk of bias ratings**

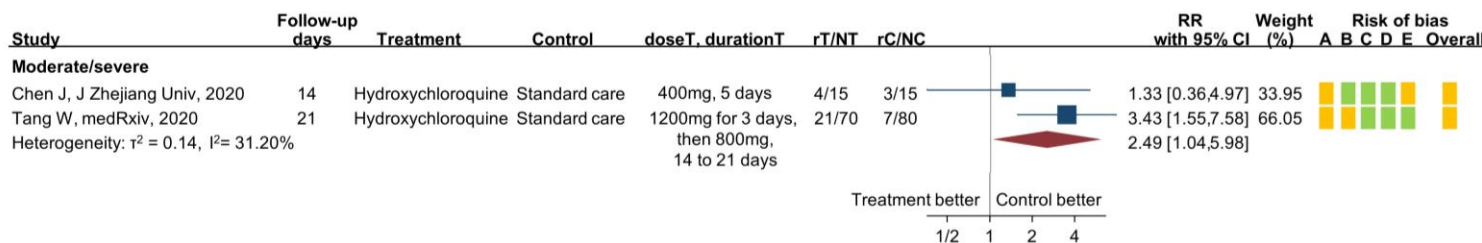
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Risk of bias domains

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 D: Bias in measurement of the outcome
 E: Bias in selection of the reported results

⊕○○○
VERY LOW

Adverse events D14-D28

**Risk of bias ratings**

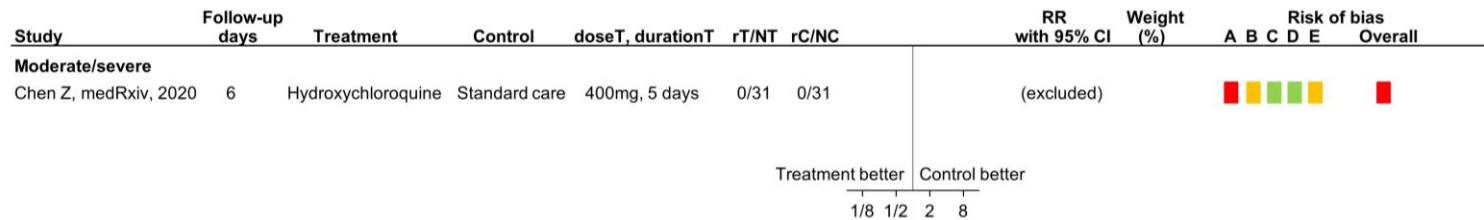
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Risk of bias domains

A: Bias arising from the randomization process
 B: Bias due to deviations from intended interventions
 C: Bias due to missing outcome data
 D: Bias in measurement of the outcome
 E: Bias in selection of the reported results

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VERY LOW

Serious adverse events D7



Risk of bias ratings

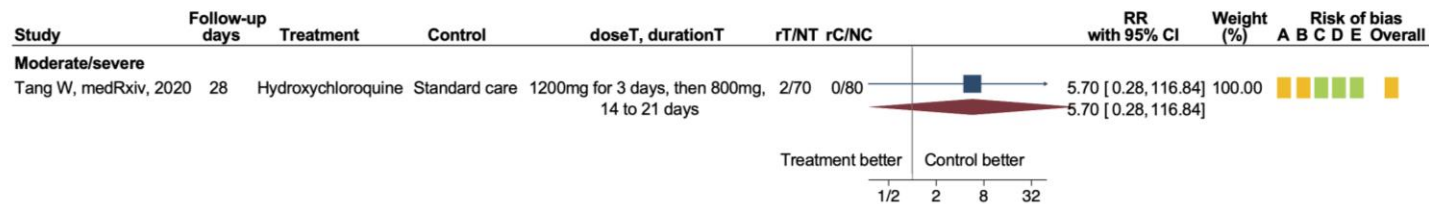
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Risk of bias domains

A: Bias arising from the randomization process
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 C: Bias due to missing outcome data
 D: Bias in measurement of the outcome
 E: Bias in selection of the reported results

⊕○○○
VERY LOW

Serious adverse events D14-D28



Risk of bias ratings

■ = low risk of bias, ■ = some concerns, ■ = high risk of bias

Risk of bias domains

A: Bias arising from the randomization process
 B: Bias due to deviations from intended interventions
 C: Bias due to missing outcome data
 D: Bias in measurement of the outcome
 E: Bias in selection of the reported results

⊕○○○
VERY LOW

References

Included RCTs

ChiCTR2000029868

Tang Wei, Cao Zhujun, Han Mingfeng, Wang Zhengyan, Chen Junwen, Sun Wenjin et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ* 2020; 369:m1849

Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, Wu Y, Xiao W, Liu S, Chen E, Chen W. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. *MedRxiv*. 2020.04.10.20060558; doi: <https://doi.org/10.1101/2020.04.10.20060558>

NCT04261517

Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L, Ling Y, Huang D, Song S, Zhang D, Qian Z. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. *Zhejiang da xue xue bao. Yi xue ban= Journal of Zhejiang University Medical sciences*. 2020 May 25;49(2):215.

ChiCTR2000029559

Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, Zhuang R, Hu B, Zhang Z. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *MedRxiv*. 2020.03.22.20040758; doi: <https://doi.org/10.1101/2020.03.22.20040758>

Included quasi-experimental studies

Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, Labella A, Manson D, Kubin C, Barr RG, Sobieszczyk ME. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. *New England Journal of Medicine*. 2020 May 7.

Mahévas M, Tran VT, Roumier M, Chabrol A, Paule R, Guillaud C, Fois E, Lepeule R, Szwebel TA, Lescure FX, Schlemmer F. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ*. 2020 May 14;369.

Mahevas M, Tran VT, Roumier M, Chabrol A, Paule R, Guillaud C, Gallien S, Lepeule R, Szwebel TA, Lescure X, Schlemmer F. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. *MedRxiv*. 2020 Jan 1.

Other references

Boutron I, Chaimani A, Devane D, Meerpohl JJ, Tovey D, Hróbjartsson A, Ravaud P. (2020, May 11). Interventions for preventing and treating COVID-19: protocol for a living mapping of research and a living systematic review. *Zenodo*. <http://doi.org/10.5281/zenodo.3820266>

Schünemann HJ, Higgins JP, Vist GE, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. *Cochrane Handb Syst Rev Interv*. John Wiley & Sons, Ltd; 2019. p. 375–402.

Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: l4898.

Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JPT. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. *BMJ* 2016; 355: i4919; doi: 10.1136/bmj.i4919.

WHO Working Group on the Clinical Characterization of COVID-19 infection. A Candidate Core Outcome Measure Set for Clinical Research During the SARS-CoV-2/COVID-19 Pandemic. submitted.

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials*. 1986 Sep 1;7(3):177-88.

Report Contributors

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Appendix 1. GRADE Working Group grades of evidence

In GRADE, a body of evidence from randomised trials begins with a high-certainty rating while a body of evidence from non-randomised studies of interventions (NRSI) begins with a low-certainty rating. The lower rating with NRSI is the result of the potential bias induced by the lack of randomization (i.e. confounding and selection bias).

However, when using the new Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool (Sterne 2016), an assessment tool that covers the risk of bias due to lack of randomization, all studies may start as high certainty of evidence (Schünemann 2018). The approach of starting all study designs (including NRSI) as high certainty does not conflict with the initial GRADE approach of starting the rating of NRSI as low certainty evidence. This is because a body of evidence from NRSI should generally be downgraded by two levels due to the inherent risk of bias associated with the lack of randomisation, namely confounding and selection bias.

GRADE assessments of certainty are determined through consideration of five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias (see table below).

The overall certainty of the evidence for each outcome can be:

- High certainty: further research is very unlikely to change our confidence in the estimate of effect
- Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low certainty: we are very uncertain about the estimate.

<p>Reasons for considering <u>downgrading</u> the certainty of the evidence:</p> <ul style="list-style-type: none"> • Limitations in study design or execution (risk of bias) • Inconsistency of results • Indirectness of evidence • Imprecision • Publication bias 	<p>Reasons for considering <u>upgrading</u> the certainty of the evidence:</p> <ul style="list-style-type: none"> • If the pooled estimates reveal a large magnitude of effect • Dose-response gradient
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For further details, see the [GRADE handbook](#) and the [Cochrane Handbook](#), Chapter 14. Chapter 14: Completing ‘Summary of findings’ tables and grading the certainty of the evidence.

Appendix 2. Observational studies

Below we provide a narrative summary of observational studies reporting on treatment of COVID-19 with hydroxychloroquine or chloroquine. Only information related to outcomes of mortality, arrhythmia, QT interval prolongation, and ventricular fibrillation resulting in sudden death are tabulated. Links to these studies are available from the living systematic review website <http://covid-nma.com>.

Mortality

Study, design, country	Intervention(s)	Participants	Outcome	Results
Carlucci 2020 Retrospective comparative observational study USA	Hydroxychloroquine and azithromycin plus zinc versus hydroxychloroquine and azithromycin alone	932 patients with COVID-19	Expired/Hospice	54/411 (13.1%) in hydroxychloroquine and azithromycin plus zinc group; 119/521 (22.8%) in hydroxychloroquine and azithromycin alone group.
Chorin 2020 Retrospective cohort USA	Hydroxychloroquine/azithromycin combination	84 adult patients with SARS-CoV-2 infection	Mortality	Four patients died from multi-organ failure, without evidence of arrhythmia and without severe QTc prolongation. 64 patients remained admitted and 16 patients were discharged.
Gautret 2020 Non-randomized clinical trial France	Hydroxychloroquine, 600mg, with or without azithromycin vs. Controls	42 patients with COVID-19	Mortality	One patient treated with hydroxychloroquine died on day 3
Kim 2020 Retrospective cohort South Korea	Hydroxychloroquine plus antibiotics (n = 22), lopinavir-ritonavir plus antibiotics (n = 35), or conservative treatment (n = 40)	270 patients with COVID-19	Mortality	None in the hydroxychloroquine group, none in the other groups
Million 2020 Retrospective cohort France	Hydroxychloroquine (200 mg three times daily for ten days) and azithromycin (500 mg on day 1 followed by 250 mg daily for the next four days)	1061 patients with COVID-19	Mortality	8 died (0.75%) (74-95 years old). All deaths resulted from respiratory failure and not from cardiac toxicity.

Molina 2020 Case series, consecutive France	Hydroxychloroquine (600 mg/d for 10 days) and azithromycin (500 mg day 1 and 250 mg days 2 to 5)	11 patients with severe COVID-19	Mortality	Within 5 days, one patient died
Rosenberg 2020 Retrospective cohort USA	Exposures: both hydroxychloroquine and azithromycin (n=735), hydroxychloroquine alone (n=271), azithromycin alone (n=211), or neither (n=221)	1438 patients with COVID-19	In-hospital mortality	The probability of death for patients receiving hydroxychloroquine + azithromycin was 189/735 (25.7% [95% CI, 22.3%-28.9%]), hydroxychloroquine alone, 54/271 (19.9% [95% CI, 15.2%-24.7%]), azithromycin alone, 21/211 (10.0% [95% CI, 5.9%-14.0%]), and neither drug, 28/221 (12.7% [95% CI, 8.3%-17.1%]). In adjusted Cox proportional hazards models, compared with patients receiving neither drug, there were no significant differences in mortality for patients receiving hydroxychloroquine + azithromycin (HR, 1.35 [95% CI, 0.76-2.40]), hydroxychloroquine alone (HR, 1.08 [95% CI, 0.63-1.85]), or azithromycin alone (HR, 0.56 [95% CI, 0.26-1.21]).
Yu 2020 Retrospective cohort China	Hydroxychloroquine (200 mg twice a day for 7–10 days) + basic treatments including antiviral drugs and antibiotics (n=48) vs. basic treatments including antiviral drugs and antibiotics (n=502)	550 critically ill COVID-19 patients (on mechanical ventilation)	Fatalities	fatalities are 18.8% (9/48) in HCQ group, which is significantly lower than 47.4% (238/502) in the NHCQ group (P<0.001).

Arrhythmia

Study, design, country	Intervention(s)	Participants	Outcome	Results
Kim 2020 Retrospective cohort South Korea	Hydroxychloroquine plus antibiotics (n = 22), lopinavir-ritonavir plus antibiotics (n = 35), or conservative treatment (n = 40)	270 patients with COVID-19	Tachycardia	One event in the hydroxychloroquine group, none in the other groups
Million 2020 Retrospective cohort France	Hydroxychloroquine (200 mg three times daily for ten days) and azithromycin (500 mg on day 1 followed by 250 mg daily for the next four days)	1061 patients with COVID-19	Rhythmic cardiac events	No rhythmic cardiac events or sudden deaths were observed.

Rosenberg 2020 Retrospective cohort USA	Exposures: both hydroxychloroquine and azithromycin (n=735), hydroxychloroquine alone (n=271), azithromycin alone (n=211), or neither (n=221)	1438 patients with COVID-19	Abnormal electrocardiogram findings, arrhythmia	Abnormal ECG findings were more common among patients receiving hydroxychloroquine + azithromycin and hydroxychloroquine alone, both overall and among those with a record of ECG screening. However, in logistic regression models of abnormal ECG findings, there were no significant differences between the groups.
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QT interval prolongation

Study, design, country	Intervention(s)	Participants	Outcome	Results
Chorin 2020 Retrospective cohort USA	Hydroxychloroquine/Azithromycin combination	84 adult patients with SARS-CoV-2 infection	Change in the QT interval; prolongation of the QTc	In 30% of patients QTc increased by greater than 40ms. In 11% of patients QTc increased to >500 ms, representing high risk group for arrhythmia.
Mercuro 2020 Retrospective cohort USA	Hydroxychloroquine with (n=53) or without azithromycin	90 patients with COVID-19	QTc prolongation	Those receiving concomitant azithromycin had a greater median (interquartile range) change in QT interval (23 [10-40] milliseconds) compared with those receiving hydroxychloroquine alone (5.5 [-15.5 to 34.25] milliseconds; P = .03). Seven patients (19%) who received hydroxychloroquine monotherapy developed prolonged QTc of 500 milliseconds or more, and 3 patients (3%) had a change in QTc of 60 milliseconds or more. Of those who received concomitant azithromycin, 11 of 53 (21%) had prolonged QTc of 500 milliseconds or more and 7 of 53 (13 %) had a change in QTc of 60 milliseconds or more.
Million 2020 Retrospective cohort France	Hydroxychloroquine (200 mg three times daily for ten days) and azithromycin (500 mg on day 1 followed by 250 mg daily for the next four days)	1061 patients with COVID-19	QTc prolongation	Nine patients had a QTc prolongation of more than 60 ms from baseline but no patient exceeded 500 ms, which corresponds to the threshold contraindicating treatment.
Molina 2020 Case series, consecutive France	Hydroxychloroquine (600 mg/d for 10 days) and azithromycin (500 mg day 1 and 250 mg days 2 to 5)	11 patients with severe COVID-19	Prolongation of the QT interval	In one patient, hydroxychloroquine and azithromycin were discontinued after 4 days because of a prolongation of the QT interval from

				405 ms before treatment to 460 and 470 ms under the combination.
Ramireddy 2020 Case series USA	Azithromycin (28%), hydroxychloroquine (10%) or a combination (62%)	490 COVID-19 positive/suspected patients	Critical QTc prolongation (a) maximum QTc ≥ 500 ms (if QRS < 120 ms) or QTc ≥ 550 (if QRS ≥ 120 ms) and b) increased QTc of ≥ 60 ms)	Significant prolongation was observed only in men (18 ± 43 ms vs -0.2 ± 28 ms in women, $p=0.02$). 12% of patients reached critical QTc prolongation. Changes in QTc were highest with the combination compared to either drug, with many-fold greater prolongation with the combination vs. azithromycin alone (17 ± 39 vs. 0.5 ± 40 ms, $p=0.07$).
Rosenberg 2020 Retrospective cohort USA	Exposures: both hydroxychloroquine and azithromycin (n=735), hydroxychloroquine alone (n=271), azithromycin alone (n=211), or neither (n=221)	1438 patients with COVID-19	Abnormal electrocardiogram findings, QT prolongation)	Abnormal ECG findings were more common among patients receiving hydroxychloroquine + azithromycin and hydroxychloroquine alone, both overall and among those with a record of ECG screening. However, in logistic regression models of abnormal ECG findings, there were no significant differences between the groups.

Ventricular fibrillation sudden death

Study, design, country	Intervention(s)	Participants	Outcome	Results
Million 2020 Retrospective cohort France	Hydroxychloroquine (200 mg three times daily for ten days) and azithromycin (500 mg on day 1 followed by 250 mg daily for the next four days)	1061 patients with COVID-19	Sudden deaths	No rhythmic cardiac events or sudden deaths were observed.
Rosenberg 2020 Retrospective cohort USA	Exposures: both hydroxychloroquine and azithromycin (n=735), hydroxychloroquine alone (n=271), azithromycin alone (n=211), or neither (n=221)	1438 patients with COVID-19	Death due to cardiac arrest	Of participants with a known cause of death: 35/118 (29.7%) in hydroxychloroquine + azithromycin group; 14/38 (36.8%) in hydroxychloroquine group; 5/17 (29.4%) in azithromycin group.