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Hydroxychloroquine is Effective and Safe for the Treatment of COVID-19, and May be Universally Effective When Used Early Before Hospitalization: A Systematic Review

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Conclusions Hydroxychloroquine has been shown to have **consistent** clinical efficacy for COVID-19 when it is used early in the outpatient setting, and in general would appear to work better the earlier it is used. **Overall HCQ is effective against COVID-19.**

There is no credible evidence that HCQ results in worsening of COVID-19. HCQ has been shown to be safe for the treatment of COVID-19 when responsibly used.

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Abstract and Figures

INTROUCTION Hydroxychloroquine (HCQ) has shown efficacy against COVID-19 in some but not all studies. We hypothesized that systematic review would show HCQ to be: effective against COVID-19, more effective used earlier, not associated with worsening, and safe.

METHODS We searched PubMed, Cochrane, EmBase, Google Scholar, and Google for all reports on hydroxychloroquine as a treatment for COVID-19 patients. This included pre-prints and preliminary reports on larger COVID-19 studies. We examined the studies for efficacy, time of administration and safety.

RESULTS HCQ was found consistently effective against COVID-19 when used early, in the outpatient setting. It was found overall effective. No credible study found worse outcomes with HCQ use. No mortality or other serious safety issue was found

CONCLUSIONS HCQ is consistently effective against COVID-19 when used early in the outpatient setting, it is overall effective against COVID-19, it has not produced worsening, it is safe.

Introduction

There is a need for effective treatment for COVID-19 infection. Hydroxychloroquine (HCQ), with or without azithromycin, has been found to have efficacy as a treatment for COVID-19 in some studies [1, 2], while other studies have not shown efficacy[3, 4].

Some physicians have stated that HCQ has greater efficacy if given earlier in the course of the disease[5, 6]. Several studies

showing negative efficacy have been withdrawn due to methodological improprieties [7].

We hypothesized that HCQ clinical studies would show significant efficacy more often than not for COVID-19; and that efficacy would be greater if HCQ were used earlier in the course of the disease. We also hypothesized that some studies that failed to show efficacy would be biased against positive efficacy and that no unbiased studies would show worsening.

We also hypothesized that HCQ would be found to be safe. Methods We searched PubMed, Cochrane, EmBase, Google Scholar, and Google for all reports on hydroxychloroquine as a treatment for COVID-19 patients. This included pre-prints and preliminary reports on larger COVID-19 studies. We included papers with HCQ alone as well as in combination with Azithramycin and/or Zinc. We excluded papers that studied Chloroquine. While Chloroquine has shown efficacy it has a higher side effects profile than HCQ. For this reason, and because HCQ is inexpensive and widely available we believe that future treatment will and should focus on HCQ. It was thus our priority to examine HCQ as fully as possible. We excluded papers that only examined hydroxychloroquine as a means to decrease transmission of coronavirus since our focus was on demonstrated clinical efficacy.

Reports were analyzed for efficacy, type of study, time of intervention with HCQ during the COVID-19 disease course, and for adverse events. Our final search was performed August 3rd, 2020.

Results

A total of 43 reports were found that examined hydroxychloroquine treatment for COVID-19 patients. 25 found

positive clinical efficacy from using hydroxychloroquine for COVID-19 patients; 15 showed no improvement with HCQ, and 3 showed worse clinical results in patients who received HCQ. 11 of the studies found in our review examined HCQ efficacy on patients in the outpatient or “day hospital” and all reported positive results [8].

However in two of the studies [9, 10] the positive results, while clinically important (decreased risk of hospitalization and improvement in symptom resolution), were not statistically significant. We found 32 reports of HCQ treatment in hospitalized patients with COVID-19. Of these 32 reports of hospitalized patients, 14 reported good results, 15 reported no improvement and 3 reported worse results. 14 studies reported the time during treatment at which HCQ was initiated.

In nine studies HCQ was administered within 48 hours of admission. In six [11-16] of these nine, improvement was noted. In three it was not [3, 17, 18]. In five studies HCQ was administered more than 48 hours after admission or in the ICU. In two [19, 20] of these five improvement was noted. In three it was not [21-23]. In 18 studies the time of administration was not specified. Seven of the 43 total studies [12, 17, 20, 24-27] were chartless retrospective studies that used only billing codes.

These studies all allowed initiation of HCQ treatment at times that differed with initiation of the control treatment: with HCQ presumably being chosen at the physician’s discretion in worsening patients more in need of treatment. All such studies were felt to exhibit selection bias against a positive result. Four additional studies [9, 10, 15, 16] had positive trends toward efficacy that did not reach statistical significance.

In 1 study [22] 8% of the treatment group was untreated but not

excluded from the treatment group calculations. In addition the median level of treatment was only 67% of the specified treatment. This large undertreatment of the treatment group was also felt to bias against a positive result. 19 of the 43 papers were pre-prints or otherwise not peer reviewed, 24 of the papers were from peer reviewed journals.

Of the eleven outpatient papers, all of which showed positive results, 7 were peer reviewed, 4 were not. Of the 32 hospitalization papers 17 were peer reviewed and 15 were not. Overall 12 of 24 or 50% of the peer reviewed papers, and 11 of 19 or 58% of the non-peer reviewed papers showed positive efficacy.

Some studies used HCQ alone, some had the addition of azithromycin or zinc. No outcome difference was seen with the addition of azithromycin (table 4). There were no deaths reported as a result of HCQ, azithromycin or Zinc treatment. Increased QTc was seen but not Torsades de Pointes. Adverse events that were felt to be likely due to HCQ treatment were non-life threatening. All were generally self limited adverse events that typically occur with HCQ. No permanent sequelae were described. Adverse events are listed in Tables 1-3.

Table 1

Table 1- Studies that showed positive results with HCQ

Study	Number of patients and treatments	Total HCQ dosage	Peer Reviewed ?	Type of Study	Severity of Cases	Treatment Initiation	Adverse Events	Results
Ahmad 2020 [28]	54 total patients- all received HCQ + AZ	average 3,700 mg	No	retrospective case series	high risk long term care facility patients	NA	1 patient had a seizure, HCQ was discontinued, does not report whether HCQ was likely cause	showed a 44% reduction in hospitalization among patients compared to a similar patient population
Arshad 2020 [12]	2,541 total patients- 1202 received HCQ, 783 received HCQ+ AZ, 1202 received AZ= 1202, usual care= 409	2,800 mg	Yes	retrospective observational study- chartless	Hospitalized patients	Started 1 day after hospitalization on average, 91% received treatment within 48 hours.	1 AE reported: prolonged QT interval on ECG	18.1% mortality for entire cohort- 13.5% mortality for HCQ alone vs 20.1% HCQ + AZ vs 22.4% just AZ vs 26% mortality for usual care.
Ashraf	100 total patients,	400 mg	No	"comprehens	hospitalized	NA	No AEs reported	Hydroxychloroquine associated

Study	Number of patients and treatments	Total HCQ dosage	Peer Reviewed ?	Type of Study	Severity of Cases	Treatment Initiation	Adverse Events	Results
Bernaola 2020 [30]	1,645 total patients, 1498 received HCQ +/- AZ	NA	No	Retrospective observational study	Hospitalized patients	NA	No AEs reported	Only Prednisone or HCQ showed a decrease in mortality after propensity- score matching. Only HCQ showed an improvement in mortality before propensity matching.
Carlucci 2020 [31]	932 total patients- 411 recieved HCQ + AZ + Zn, 521 received HCQ + AZ	2400 mg	No	retrospective observational study	Hospitalized patients	NA	No AEs reported	Addition of zinc to regimen associated with decreased mortality, hospice, or ventilator rates. Effect driven by non critical patients.
Chen 2020 [11]	62 total patients- 31 received HCQ, 31 received usual care	2000 mg	No	prospective randomized clinical trail	Hospitalized patients- severe and critical infections excluded	Started 1 day after hospitalization	1 rash, 1 headache reported. No severe AEs reported	Time to clinical recovery, body temp recovery time, and cough remission time significantly shortened in the HCQ group. The 4 patients that progressed to severe illness all in usual care group
Davido 2020 [13]	132 total patients, 52 received HCQ and AZ	5,800 mg average	Yes	Retrospective observational study	Hospitalized patients	average initiation 0.7 days after hospitalization	1 AE reported: prolonged QT interval on ECG	Reduction in unfavorable outcome in patients receiving HCQ and AZ, especially patients with elevated lymphocyte or CRP levels

Study	Number of patients and treatments	Total HCQ dosage	Peer Reviewed ?	Type of Study	Severity of Cases	Treatment Initiation	Adverse Events	Results
de Novales 2020 [32]	164 total patients- 123 received HCQ, 34 received usual care	Average total dosing 3600 mg	No	retrospective cohort study	Hospitalized pts, 83 mild cases, 38 moderate cases, and 35 severe cases	NA	No AEs reported	22.2% death rate in HCQ group vs 48.8% death rate in usual treatment group. 1.8x high mean cumulative survival in mild group vs 1.4x in moderate vs 1.6x in severe. Statistically significant in mild group
Esper 2020 [8]	636 total patients, 412 received HCQ and AZ, 224 received usual care	3200 mg	No	prospective observational study	Outpatient telemedicine visits	Started an average of 5.2 days since symptom onset	2 serious AEs: maculopapular rash, and severe pruritus	Hospitalization rate of 1.9% in treatment group and 5.4$ in control group. Also saw improvement lower hospitalization rate (1.17% vs. 3.2%) for patients that started treatment before 7th day of symptoms vs after the 7th day of symptoms
Gautret 1 2020 [33]	36 total patients- 20 received hydroxychloroquine, 16 received usual care	6000 mg	Yes	prospective open-label non-randomized clinical trial	"Day hospital" patients- included 8 asymptomatic cases	NA	None reported	70% of hcq patients viral clearance after 6 days via nasal swab PCR vs 12.5% control group
Gautret 2 2020 [34]	80 total patients- all received HCQ	6000 mg	Yes	prospective uncontrolled observational study	"Day hospital" patients with mild infections	NA	2 instances of nausea/ vomiting, 4 reports of diarrhea, and 1 report of blurred vision after 5 days of treatment. None required discontinuation of treatment.	65 had favorable outcome, 15% required O2 therapy, 1 ICU admission, 1 death. PCR tests- 83% day 7, 93% day 8, 100% by day 12

Study	Number of patients and treatments	Total HCQ dosage	Peer Reviewed ?	Type of Study	Severity of Cases	Treatment Initiation	Adverse Events	Results
Guerin 2020 [2]	88 total patients- 34 patients received usual	average 5,100 mg total	Yes	retrospective cohort analysis	outpatients with mild/ moderate	Started day after symptoms	No serious AEs, 5 minor events including,	Both AZ and HCQ + AZ, showed a significant improvement in recovery time compared to

	care, 34 patients received AZ, and 20 received HCQ + AZ	dosage			COVID-19	for 36 patients, within 15 days for the rest.	urticarea, headach, nausea, and vomiting.	usual care (9.2, 12.9, and 25.8 days respectively)
Kim, JW 2020 [35]	65 total patients, 31 received lopinavir-ritonavir, 24 received HCQ, 26.5% of HCQ patients also received AZ	minimum 2800 mg	Yes	retrospective cohort study	hospitalized patients	average duration of symptoms before initiation was 7 days	1 report of respiratory failure and 1 report of shock in HCQ group (likely from COVID-19 not treatment)	HCQ group saw slower viral clearance time compared to lopinavir-ritonavir group but saw equivalent time to remission of symptoms
Kim, MS 2020 [36]	97 total patients, 22 received HCQ +/- AZ, 35 received Lopinavir-ritonavir, 40 received usual care	200 mg 2x daily, duration not reported	No	retrospective cohort study	moderate hospitalized cases	NA	No serious adverse events reported. 20 reports of abdominal/ GI adverse events	Patients treated with HCQ saw improved viral clearance, shorter hospital stays, and quicker cough symptom resolution.
Lagier 2020 [37]	3,737 total patients- 3,119 received HCQ + AZ, 618 received usual care	6000 mg	Yes	retrospective observational study	Hospitalized patients and patients seen at a "Day-Care Hospital".	Started one day after positive testing	12 patients had HCQ discontinued due to QT prolongation. 3 cases of QTc > 500 ms. No cases of Torsades de Pointes or sudden	Treatment w/ HCQ-AZ associated with decreased risk of ICU transfer, decreased risk of extended hospitalization, and decreased risk of death.

Study	Number of patients and treatments	Total HCQ dosage	Peer Reviewed ?	Type of Study	Severity of Cases	Treatment Initiation	Adverse Events	Results
Million 2020 [6]	1061 patients- all received HCQ + AZ	6000 mg	Yes	retrospective observational study	Hospitalized patients and patients seen at a "Day-Care Hospital"	Started within 2 days after positive testing	25 mild adverse events reported, no serious AEs	4.6 % poor clinical outcome (death, transfer to ICU, or hospitalization for 10 days or more). 20 of 21 repeat nasal swabs were negative by day 15 post treatment.
Monfort e 2020 [1]	539 total patients, 197 received HCQ, 94 received HCQ + AZ, 92 received usual care	NA	Yes	Retrospective study- not randomized	Hospitalized patients	NA	No AEs reported	Mortality rates of 27% with HCQ, 23% with HCQ + AZ, and 51% with usual care. Mechanical ventilation rates of 4.3% in HCQ, 14.2% in HCQ + AZ, and 26.1% with usual care. After adjusting for confounders, HCQ + AZ associated with a 66% reduction in risk of death compared to usual care
Sbidian 2020 [38]	4,642 total patients, 623 received HCQ, 227 received HCQ + AZ	NA	No	Retrospective cohort study- chartless	Hospitalized patients	NA	No AEs reported	No difference in mortality rate found in HCQ vs usual care after regression analysis. Discharge rates significantly higher in HCQ group.
Scholz 2020 [39]	141 total patients all received HCQ, AZ, and ZN	2000 mg	No	Retrospective Case series	Outpatient cases	Average initiation of treatment 4.8 days after symptom onset	No serious AEs reported	Hospitalization rates in treated patients 84% less than community control. Decreased risk of mortality as well.

Study	Number of patients and treatments	Total HCQ dosage	Peer Reviewed ?	Type of Study	Severity of Cases	Treatment Initiation	Adverse Events	Results
Xue 2020 [14]	30 total patients, 15 received HCQ within 7 days of hospitalization, 15 after 7 days	minimum 2,000 mg	Yes	Retrospective cohort study	Hospitalized patients	either before 7 days or after 7 days of hospitalization	No AEs reported	Patients treated with HCQ earlier recovered faster than patients in later group, and less rates of mechanical ventilation and ICU transfer
Yu 2020[20]	568 total patients critcially ill (ventilated, septic shock, ICU/ organ failure) covid patients. 48 patients received HCQ, 520 usual care	average 3,400 total mg	Yes	retrospective cohort study/	Hospitalized patients- all critically ill (including patients in the ICU, ventilated, or in septic shock)	NA	No AEs reported	18.8% death rate in HCQ group vs 45.8% in usual care group. Cox regression analysis showed significantly decreased mortality risk in HCQ group. Also showed significant decrease in Il-6 after HCQ application, no change in control group.
Yu 2020 letter to editor [19]	2,882 total patients, 278 received HCQ	average 3,400 total mg	Yes	retrospective cohort study- chartless	hospitalized patients	median time to HCQ administration 10 days after hospitalization	No AEs reported	HCQ group saw reduced levels of IL-6, improvement in albumin, troponin I, and BNP levels in patients treated with HCQ. Also saw a reduction in mortality rates in COVID-19 patients with cardiac injury

Table 2

Table 2- Studies that showed no improvement with HCQ

Study	Number of patients and treatments	Total HCQ dosage	Peer Reviewed ?	Type of Study	Severity of Cases	Treatment Initiation	Adverse Events	Results
An 2020 [21]	226 total patients, 31 received HCQ, AZ +/- to physician discretion	3,400 mg average	No	Retrospective nonrandomized cohort study	Hospitalized patients- target population "mild to moderate cases"	Average initiation 6.7 days after diagnosis	No severe Adverse events reported	After propensity score matching and cox regression analysis found that HCQ was not associated with better clinical outcomes like viral clearance, length of hospital stay, and duration of symptoms.
Cavalcanti 2020 [4]	667 total patients,217 receied HCQ + AZ, 221 received HCQ, and 229 received standard care	5,600 mg bid	Yes	prospective randomized controlled trial	hospitalized with mild/ moderate cases	NA, gives time to group assignment, not time to treatment initiation	30 reports of increased QTc, 6 reports of arrhythmia	No significant difference in 15 day outcome between HCQ, HCQ + AZ, and usual care
Geleris 2020 [17]	1446 total patients- 70 intubated initially, 811 received HCQ,	average of 3,200 mg	Yes	Retrospective cohort- chartless	Hospitalized patients	Started within 24 hours after hospitalization	No AEs reported	no significant difference between HCQ use and intubation or death, +/- azithromycin also no change
Giacomelli 2020 [40]	172 patients, 43 received HCQ + LPV/ritonavir within 5 days of symptoms and 129 after 5 days of symptoms	2,000 mg - 8,000 mg (200 mg bid for 5-20 days)	No	Retrospective nonrandomized cohort study	hospitalized patients	either before or after 5 days of symptoms	Increase in hepatic enzymes, nausea, an diarrhea reported, attributed to LPV/r.	No difference between groups in mortality rates after adjusting for co-morbidities

Study	Number of patients and treatments	Total HCQ dosage	Peer Reviewed ?	Type of Study	Severity of Cases	Treatment Initiation	Adverse Events	Results
Ip 2020 [24]	2512 total patients, 1914 received HCQ, and 59% of HCQ patients received AZ.	2,600 mg	No	Retrospective cohort study- chartless	Hospitalized patients not Discharged home within 24 hrs.	NA	Prolonged QTc or arrhythmia reported in 134 patients. Cardiomyopathy reported in 20 patients. Does not comment on whether these were related AEs.	no signicant differnce between HCQ and standard care group. 30 day mortality for standard care was 0.2, vs any HCQ 0.2, vs HCQ +AZ 0.18.
Kalligeros 2020 [41]	108 total patients, 36 received hydroxychloroquine +/- AZ, 72 received usual care	NA, 5 days of treatment with HCQ, but does not give dosage	Yes	retrospective cohort study	hospitalized patients	NA	2 reports of QTc prolongation, 1 report of altered mental status, no reports of torsades de pointes	After regression analysis, no significant improvement in mortality rates, hospitalization duration, or time to clinical improvement
Lopez 2020 [23]	29 total patients, 17 patients with on target HCQ levels, and 12 patients with HCQ below target levels. All received AZ as well	4,400 mg	Yes	retrospective cohort study	ICU patients	NA	Abnormal EKGs reported in 7 patients. All discontinued treatment.	no significant difference in 15 day mortality rate or discharge from the ICU from patients reaching HCQ level goals and not

Study	Number of patients and treatments	Total HCQ dosage	Peer Reviewed ?	Type of Study	Severity of Cases	Treatment Initiation	Adverse Events	Results
Mahevas 2020 [16]	29 total patients, 17 patients with on target HCQ	600 mg/ day, does not give	No	retrospective cohort study	hospitalized patients requiring	Started within 48 hrs after	8 patients discontinued HCQ due to EKG	No statistically significant difference in poor clinical outcomes. 20.5% of pts in HCQ

	levels, and 12 patients with HCQ below target levels. All received AZ as well	duration of treatment			oxygen therapy	hospitalization	changes. 1 report of a QTc > 500 ms	transferred to ICU or died w/in 7 days, 22.1% for control. 2.8% of pts in HCQ group died w/in 7 days vs 4.6% control. ARDS in 27.7% HCQ group vs 24.1% control
Mallat 2020 [3]	34 total patients- 21 received HCQ	4,800 mg	No	retrospective observational study	Hospitalized patients- intensive care unit patients and ventilator patients excluded	Started within 2 days after hospitalization. Median administration of HCQ at 0 days from hospitalization.	No AEs reported	Hospital stay longer for HCQ group vs standard care, but non-significant. Main outcome: time to negativity longer for HCQ patients 17 vs 10 days for non HCQ patients. Also showed no improvement in inflammatory markers/ lymphopenia in HCQ group.
Mitja 2020 [9]	353 total patients, 169 received HCQ, 184 received usual care	3,200 mg	Yes	prospective randomized controlled trial	outpatients	average time from symptom onset to treatment initiation was 3 days	No treatment related SAEs. Multiple reports of nausea vomiting, and headaches.	no difference in viral clearance and no improvement in risk of hospitalization compared to control group
Molina 2020 [42]	11 total patients- all received HCQ + AZ	6,000 mg	Yes	Prospective non-controlled trial	Hospitalized Patients- moderate to severe infections	NA	1 report of qt prolongation, HCQ discontinued	Nasopharyngeal swabs still positive in 8/10 after treatment 5-6 days after treatment. Clinical results: 1 death, 2 ICU admissions

Study	Number of patients and treatments	Total HCQ dosage	Peer Reviewed ?	Type of Study	Severity of Cases	Treatment Initiation	Adverse Events	Results
ORCHID trial [43]	470 total patients	2,400 mg	No	prospective randomized controlled blinded study	Hospitalized patients	NA	No AEs reported	no data yet released, trial arm stopped due to "lack of efficacy"
Paccoud 2020 [15]	89 total patients- 38 pts treated with HCQ, 46 treated standard care	6,000 mg	Yes	retrospective cohort study	Hospitalized patients	Started within 2 days after hospitalization	6 AEs reported: 2 cases of QTc prolongation, cytopenia, paresthesia, headache diarrhea	no significant difference in risk for long hospital admission, ICU admission, or death between HCQ group and standard of care group
Rosenberg 2020 [18]	1438 total patients- 735 received HCQ+ AZ, 271 received HCQ alone, 211 recieved AZ alone, 221 received usual care	NA	Yes	retrospective cohort study	Hospitalized patients	Median administration of HCQ 1 day after admission, median administration of AZ 0 days after admission	194 reports of arrhythmia reported with patients receiving HCQ & 120 reported QT prolongations. No effort to determine if AEs were treatment related.	Mortality 22.5% for HCQ + azithromycin, 18.9% HCQ alone, 10.9% for azithromycin alone, 17.8% for neither drug. Differences between the groups not statistically significant
Singh 2020 [25]	3,372 total patients, 1,125 received HCQ, 799 of these patients also received AZ. 2,247 received usual care	NA	No	retrospective cohort study- chartless	Hospitalized patients	NA	No AEs reported	After propensity score matching, no significant difference in mortality rates between patients treated with HCQ and usual care.

Study	Number of patients and treatments	Total HCQ dosage	Peer Reviewed ?	Type of Study	Severity of Cases	Treatment Initiation	Adverse Events	Results
Skipper 2020 [10]	423 total patients, 212 received HCQ, 211 received placebo	3,800 mg	Yes	prospective randomized controlled trial	outpatients	treatment initiated within 4 days of symptoms	Multiple reports of abdominal pain, nausea, and diarrhea. No SAEs related to treatment reported.	No statistically significant improvement of symptom severity between HCQ and placebo group, no statistically significant difference in hospitalization/ mortality between the two groups
Tang 2020 [44]	150 total patients, 75 received HCQ, 75 received usual care	12,400 mg or 18,000 mg (avg 15,200)	Yes	Prospective open label, randomized, controlled trial	hospitalized pts- 148 pts with mild to moderate infections, 2 patients with severe infections	NA	2 serious adverse events reported: 1 report of blurred vision, and one report of thirst Both transient and self limited	Only results on "negative conversion" presented- 2 negative PCR tests 24 hrs. Convers on rate in 28 days experimental group- 85.4%, control group- 81.3%, not statistically significant.

*AE, adverse event; AZ, Azithromycin; HCQ, hydroxychloroquine; LPV/r, lopinavir/ ritonavir ; SAE, serious adverse event; ZN, Zinc

Table 3

Table 3- Studies that showed worse results with HCQ

Study	Number of patients and treatments	Total HCQ dosage	Peer Reviewed ?	Type of Study	Severity of Cases	Treatment Initiation	Adverse Events	Results
Horby 2020 [22]	4,686 total patients- 1561 received HCQ, 3155 received usual care, 17% of HCQ patients received AZ	8,800 mg	No	prospective randomized controlled trial	Hospitalized patients	Started an average of 3 days after hospitalizati on	1 case of Torsades de Pointes, patient recovered without need for intervention	No significant difference in 28 day mortality (25.7% HCQ, 23.5% usual care). HCQ group had worse discharge and ventilation rates compared to usual care. No difference in arrhythmia rates
Magagn oli 2020 [26]	807 total patients- 158 received HCQ, and 214 recieved HCQ + AZ	median 2,000 mg	Yes	retrospective cohort study- chartless	Hospitalized patients	NA	No adverse events reported	mortality risk higher in HCQ group, no significant difference in chance of mechanical ventilation between the two groups
Rivera 2020 [27]	2,186 total patients, 538 received HCQ +/- AZ , 1321 received usual care, 327 received other medications	NA	Yes	retrospective observational study- chartless	Hospitalized patients	NA	No Aes reported	After multivariable logistic regression HCQ alone showed no improvement in mortality vs usual care. HCQ in combination with other medication was associated with an increase in mortality

*AE, adverse event; AZ, Azithromycin; HCQ, hydroxychloroquine; LPV/r, lopinavir/ ritonavir ; SAE, serious adverse event; ZN, Zinc

Table 4

Table 4- Comparison of treatments, setting, and results

	Positive Results		No Change		Negative Results	
Outpatient	9	Treatments HCQ: 2 HCQ + AZ: 7 HCQ +/- AZ: HCQ + antivirals:	2	Treatments HCQ: 2 HCQ + AZ: HCQ +/- AZ: HCQ + antivirals:	0	Treatments HCQ: HCQ + AZ: HCQ +/- AZ: HCQ + antivirals:
Hospitalized- Treated w/in 48 hrs	4	Treatments HCQ: 2 HCQ + AZ: 1 HCQ +/- AZ : 1 HCQ + antivirals:	5	Treatments HCQ: 3 HCQ + AZ: HCQ +/- AZ: 2 HCQ + antivirals:	0	Treatments HCQ: HCQ + AZ: HCQ +/- AZ: HCQ + antivirals:
Hospitalized- treated after 48 hrs or ICU pts	2	Treatments HCQ: 2 HCQ + AZ: HCQ +/- AZ: HCQ + antivirals:	2	Treatments HCQ: HCQ + AZ: 1 HCQ +/- AZ: 1 HCQ + antivirals:	1	Treatments HCQ: HCQ + AZ: HCQ +/- AZ: 1 HCQ + antivirals:
Administration time not reported in relation to hospitalization	8	Treatments HCQ: 1 HCQ + AZ: 1 HCQ +/- AZ: 5 HCQ + antivirals: 1	8	Treatments HCQ: 2 HCQ + AZ: 1 HCQ +/- AZ: 4 HCQ + antivirals: 1	2	Treatments HCQ: HCQ + AZ: HCQ +/- AZ: 2 HCQ + antivirals:

Table 5

Table 5- Study results by Time of Treatment Initiation

Time of Treatment Initiation	# of Studies Showing Clinical Improvement	Number of Studies Showing no Improvement	% improved vs total studies
Outpatient*	11	0	100%
Within 48 hours after hospitalization*	6	3	67%
After 48 hours of hospitalization or ICU patients	2	3	40%
Non-specified inpatient studies	8	10	44%
Total	27	16	63%

*Both the outpatient and w/in 48 hrs of hospitalization groups each had 2 studies that trended towards positive results but did not achieve statistical significance. This table has these studies grouped with the good results

Discussion

This study has four important findings. The first is that HCQ appears to be consistently effective for the treatment of COVID-19 when used early in the course of disease in the outpatient setting, and is generally more effective the earlier it is used. The second is that overall HCQ has had efficacy against COVID-19 in a majority of studies. The third is that there are no unbiased studies showing a negative effect of HCQ treatment of COVID-19. The fourth is that HCQ appears to be safe for the treatment of COVID-19 when used responsibly.

TIMING OF HCQ USE: It was striking that 100% of the 11 of the studies which used HCQ early in the disease on an outpatient basis showed positive results. In two of the studies [9, 10] the benefit was only a trend. However the effects were clinically important: in Mitja's study resolution of symptoms was decreased from 12 to 10 days; In Skipper's study the rate of hospitalization was decreased by 60%. It is likely that with higher powering statistical significance would have been reached. In the 32 other studies HCQ was given on an inpatient basis with more advanced disease. The studies were divided into early, late and ICU administration times. The early use, within 48 hours of admission showed 6 of 9 or 67% of the studies to have

positive efficacy. The two later groups, after 48 hours admission and in the ICU showed 2 of 5 or 40% to have positive efficacy. Thus, from 100% for early outpatient, to 67% for early hospital, to 40% for later hospital use, there appears to be a relationship with time of initiation of treatment, and better results the earlier HCQ is used.

OVERALL EFFICACY: 23 of the 43 studies (53%) showed a definite positive effect of HCQ vs COVID-19. However if negatively biased studies are removed and the clinically important positive trends from underpowered studies are moved to the positive efficacy group the ratio changes to 28 positive vs 9 no effect: a 75% positivity ratio of positive HCQ studies. Interestingly none of the no-effect studies showed a clear trend toward worsening.

RANDOMIZED CONTROLLED STUDIES (RCTs): Of the seven RCTs two [9, 10] were in the outpatient early treated group. As described above both studies had clinically important trends toward positive results, although were underpowered and did not reach statistical significance. The other five RCTs were in hospitalized patients later in disease where efficacy seems to be less. There was 1 positive [11], 3 no-effect [4, 43, 44], and 1 negative effect [22] studies. The negative effect study, however, was biased, as described below (“negative effect studies”), such that any negative or no-effect result would not be valid. Thus two of two RCTs with early treatment showed positive results, and one of three hospitalized patients had a positive result, consistent with the general finding of better results with earlier use.

NEGATIVE EFFECT STUDIES: Three studies had data that seemed to show worse outcomes with HCQ use. However had significant biases. And all were in hospitalized patients when

results with HCQ are less good. Two [3, 16] of the three studies were well done studies that were nonetheless constrained by being chartless hospitalization studies that only used billing codes at particular time points to evaluate patients, but had no information as to events between these time points within their hospital course which led to initiation of treatment. Both were retrospective. Patients were not randomized to treatment with HCQ versus other care.

Rather patients apparently received HCQ at the discretion of the physician The time of administration of HCQ in the patients who received it was not specified during the hospitalization. This introduces selection bias in both studies toward treatment with HCQ for sicker patients who were faring worse after admission who presumably would be more likely to have treatment selected by their physician.

Attempting to normalize co-morbidities does not correct this bias because clinical progress of COVID-19 infection is not well predicted by pre-existing co-morbidities. This selection basis means patients who worsened after admission who are thereby more likely to have worse outcomes would be over represented in the HCQ treatment group.

For this reason negative results from the treatment arm of these studies are not valid because outcomes are moved negatively. A positive effect however would have validity since it could only occur despite the negative selection bias, not because of it.

The third study showing worse results with HCQ was a highly powered non-peer reviewed study whose primary outcome of 28 day mortality actually showed no difference between the HCQ treated group and the usual treatment group. Two of the secondary results did just barely reach significance negatively.

[22]. However the reporting of results was flawed as follows. 8% of the treatment group patients did not receive HCQ at all; and the median number of days of treatment for all treated patients was only 6 out of a prescribed 9.

These facts mean that less than half of patients received the full treatment regimen or even two thirds of the full treatment regimen, with 1 in 12 receiving no treatment at all. These untreated and undertreated patient outcomes were however grouped with the fully treated patient outcomes.

If HCQ has any positive effect which we believe it is well established, this undertreatment would invalidate their borderline negative secondary results. In addition treatment was initiated more than 48 hours after admission when our aggregate data has shown a high incidence of no-effect results.

The study was not blinded introducing a potential undertreatment bias toward patients who were known by the staff to be treated with HCQ. This study most reasonably is actually a no effects study, which is common in already hospitalized patients such as these treated more than 48 hours after admission.

ADVERSE EVENTS: There have been fears among some that the increased QTc seen in some patients treated with HCQ or azithromycin would predispose to Torsades de Pointes (TDP) and then death from ventricular fibrillation. We found no such deaths, or death from any cause related to HCQ treatment, and indeed only 1 case of TDP at all – which resolved spontaneously without treatment and without sequelae.

All of the adverse events which seemed attributable to HCQ treatment in the 43 studies were typical side effects commonly seen with HCQ. These included nausea, vomiting, diarrhea,

stomach pain, headache, rash, dizziness, itching and blurred vision. In all cases there was no indication of persistence of symptoms after discontinuance of the HCQ.

HCQ has been used with great safety for more than 50 years, and the relatively minor adverse events seen in these studies is consistent with this high safety profile.

STRENGTHS AND WEAKNESSES: A strength of this study is the large number of cohorts. A further strength is the critical methodological study analysis heretofore not attempted to our knowledge for these studies.

One weakness is the heterogeneity of study designs which rendered comparison of study results challenging. Another perceived weakness of the study could be that these include reports made outside of peer-reviewed literature. Multiple papers reporting both improvement and no efficacy using hydroxychloroquine that have been included in the study are either pre-prints or preliminary results of larger trials.

Because of the unprecedented and time sensitive nature of the SARS-COV2 pandemic the scientific community has shared data and studies on a level unseen prior to this emergency. We believe that these reports hold valuable information and decided to include them regardless of the way in which they were published.

In addition we found that both the peer-reviewed and non-peer reviewed papers showed a similar breakdown between studies showing efficacy vs not so that bias was not introduced.

SIGNIFICANCE: We believe our findings have substantial societal global importance since there have been numerous edicts either preventing HCQ use for COVID-19 or limiting it to the inpatient setting which we believe have resulted in many

unnecessary deaths.

Our findings showing efficacy and safety of HCQ against COVID-19 indicate that HCQ should be freely available to patients and physicians who choose to use it. And it should especially be freely available to be used on an outpatient basis before hospitalization where it appears to be more effective and where early fears of fatal heart arrhythmias have been shown to be unfounded[45].

This is particularly important because the only drug to show efficacy, Remdesivir, has shown no significant benefit in a recent study [46].It is also expensive and not widely available. Convalescent plasma has shown benefit [47] but even this is not well validated and plasma is not available in large numbers of doses.

Thus HCQ with proven efficacy and safety, a cost of 37 cents per pill and thus a total treatment cost of under 20 dollars[48], versus 3,100 dollars for Remdesivir[49], as well as wide supply chain availability, would appear to be the best COVID-19 treatment option available and needs to be widely promoted as such.

Unfortunately the controversies surrounding HCQ have resulted in physicians being afraid to prescribe it for reasons which have nothing to do with medicine, and in patients being afraid to take it due to spurious reports of danger, or fears that is not effective.

It is hoped that this study will disabuse the medical community of these misapprehensions about efficacy and validate that it is both efficacious and safe, and needs to be freely prescribable. Thousands of lives may lie in the balance.

We also do not believe that randomized controlled studies are necessary before HCQ is authorized for general use because

the efficacy seen in studies already done indicates that control patients in such studies might die unnecessarily; and because the time delay to do any such study would cause yet more deaths by preventing HCQ use when it is most needed – which is immediately.

Our study has shown that good evidence of efficacy exists; and there is no safety, cost, or supply reason to not treat now. Unnecessary death from delayed treatment is too high a price to pay for greater certainty of knowledge.

Many may have already died unnecessarily due to HCQ misinformation and it is imperative that we do not further add to the toll.

> **Conclusions** Hydroxychloroquine has been shown to have **consistent** clinical efficacy for COVID-19 when it is used early in the outpatient setting, and in general would appear to work better the earlier it is used. **Overall HCQ is effective against COVID-19.**
>
> There is no credible evidence that HCQ results in worsening of COVID-19. HCQ has been shown to be safe for the treatment of COVID-19 when responsibly used.

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