Compassionate use of hydroxychloroquine in clinical practice for patients with mild to severe Covid-19 in a French university hospital

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Summary: In hospitalized adults with Covid-19, no significant reduction of the risk of unfavorable outcomes was observed with hydroxychloroquine in comparison to standard of care.

Abstract

Background

Data from non-randomized studies have suggested that hydroxychloroquine could be an effective therapeutic agent against Covid-19.

Methods

We conducted an observational, retrospective cohort study involving hospitalized adult patients with confirmed, mild to severe Covid-19 in a French university hospital. Patients who received hydroxychloroquine (200mg tid dosage for 10 days) on a compassionate basis in addition to SOCwere compared to patients without contraindications to hydroxychloroquine who received SOCalone. A propensity score-weighted analysis was performed to control for confounders: age, sex, time between symptom onset and admission ≤ 7 days, Charlson comorbidity index, medical history of arterial hypertension, and obesity, NEWS2 score at admission, and pneumonia severity. The primary endpoint was time to unfavorable outcome, defined as: death, admission to an intensive care unit, or decision to withdraw or withhold life-sustaining treatments, whichever came first.

Results

Data from 89 patients with laboratory-confirmed Covid-19 were analyzed, 84 of whom were considered in the primary analysis; 38 patients treated with hydroxychloroquine and 46 patients treated with SOCalone. At admission, the mean age of patients was 66 years, the median Charlson comorbidity index was 3, and the median NEWS2 severity score was 3. After propensity score weighting, treatment with hydroxycholoroquine was not associated with a significantly reduced risk of unfavorable outcome (HR 0.90 [0.38; 2.1], p = 0.81). Overall survival was not significantly different between the two groups (HR 0.89 [0.23; 3.47], p = 1)

Conclusion

In hospitalized adults with Covid-19, no significant reduction of the risk of unfavorable outcomes was observed with hydroxychloroquine in comparison to standard of care. Unmeasured confounders may however have persisted despite careful propensity-weighted analysis and the study might be underpowered. Ongoing controlled trials in patients with varying degrees of initial severity on a larger scale will help determine whether there is a place for hydroxychloroquine in the treatment of Covid-19.

Introduction

Since December 2019, a novel coronavirus, designated SARS-CoV-2, has caused a worldwide outbreak of respiratory illness known as coronavirus 2019 disease (Covid-19). The spectrum of Covid-19 ranges from mild illness to severe progressive pneumonia, multiorgan failure, and death [1–4]. In this setting, the repurposing of drugs for use as experimental antiviral agents is of critical importance. To date, there are no specific therapeutic agents approved in the treatment of Covid-19, but the Food and Drug Administration has issued an Emergency Use Authorization on March 28th, 2020, for emergency use of hydroxychloroquine in this setting [5]. Following recent publications showing in vitro activity of hydroxychloroquine (HCQ) against SARS-CoV-2 [6,7], there are few data on the efficacy of this drug in patients with SARS-CoV-2-related pneumonia with differing levels of severity, but many trials are ongoing [8,9]. Preliminary results pooled from ongoing randomised, open, controlled studies in China reportedly showed superiority of HCQ compared to a control group (chloroquine or standard of care) in terms of reduction of exacerbation of pneumonia, duration of symptoms, and delay to viral clearance [8]. These results have led to great enthusiasm worldwide and calls for its widespread use in the treatment of SARS-CoV-2-related pneumonia. However, some of the aforementioned studies have since been cancelled or are not currently recruiting, and a recent study by Chen et al, showed no impact of HCQ on viral clearance, symptoms, or radiological progression [10]. Overall, data to support the widespread use of HCQ in the treatment of COVID-19 therefore remains inconclusive [11] . On March 11th, 2020, Gautret et al., reported 20 cases of Covid-19 patients treated with HCQ in a French hospital, showing a significant reduction of SARS-CoV-2 viral loads at day 6-post inclusion compared to controls, and much lower average duration of viral carriage than reported for untreated patients in the literature [12]. At that time, faced with an increasing influx of Covid-19 patients in our Infectious Diseases ward and before enrolment in randomized clinical trials was made available, we decided to use HCQ on a compassionate basis in our department. Until results of these randomized controlled trials are made available, new data are therefore dramatically needed about the effectiveness of HCQ. In this retrospective cohort study, we evaluated the efficacy and safety of compassionate use of HCQ in hospitalized patients with mild to severe COVID-19 infection

compared to standard of care (SOC) patients.

Methods

Study design.

This is an observational retrospective exposed-non exposed cohort study aiming at evaluating the efficacy of HCQ treatment as compared to SOC in patients hospitalized with a diagnosis of Covid-19. This article complies with the STROBE criteria.

Patients.

Eligible patients for the study were all patients hospitalized in the Infectious Diseases ward of the Pitié-Salpêtrière University hospital from January 2020 with a diagnosis of Covid-19. Patients who were admitted in the Infectious Diseases ward after a stay in an ICU were excluded from analysis, as were patients unable to provide an informed consent, those treated with another experimental treatment, and those who presented a contraindication to receiving hydroxychloroquine. These included: patients with a corrected QT interval longer than 440ms on the electrocardiogram performed at admission; those with known hypersensitivity to chloroquine or hydroxychloroquine; those with a history of elongated QT interval or severe cardiopathy, G6PD deficiency, or retinopathy; and finally patients receiving comedications known to elongate the QT interval or potentially responsible for drug-drug interactions that would require close monitoring. All patient comedications were cross-referenced with the list of medications potentially responsible for drug-drug interactions provided by the Liverpool Drug Interactions Group [13].

HCQ patients

On March 11th, 2020, physicians from the Infectious Diseases ward of the Pitié-Salpétrière University hospital collectively decided to systematically propose administering HCQ (200mg tid for 10 days) on a compassionate basis to adult patients with a diagnosis of laboratory-confirmed Covid-19 infection, based on the promising results of Chinese and French studies [8,12] . The decision to administer HCQ was ultimately left to the attending physician and the patient was informed about the rational to propose the treatment, the fact that efficacy was not proven, and about potential side effects. Only patients who agreed to receive the treatment were treated. In addition to HCQ treatment, SOC was provided (see below). Concomitant antibiotherapy could be used, which was left to the discretion of the attending physician. Due to concerns regarding the risk of cardiologic complications, azithromycin was not added to the HCQ treatment regimen with the exception of one patient.

Standard of care only patients

This group consisted of patients hospitalized before the collective decision of treating with HCQ in the ward, patients who had refused, and patients for whom the treatment was not administered (for any reason but contraindication to HCQ). SOC consisted of supplemental oxygen therapy in order to maintain an oxygen saturation of >96%, intravenous or oral acetaminophen, and antibiotics if deemed necessary. No patient received azithromycin.

Diagnosis and documentation of Covid-19 infection.

Diagnosis of Covid-19 was confirmed for all patients on the basis of a positive reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay from a nasopharyngeal swab or induced sputum sample [14]. Systematic follow-up RT-PCR were not performed for already-diagnosed Covid-19 patients, as tests were prioritized for the diagnosis of new infections.

Clinical, radiological and laboratory data

Clinical and biological variables were retrospectively collected from the medical files of all patients with laboratory-confirmed Covid-19. Baseline comorbidities and initial severity were retrospectively assessed using the Charlson comorbidity index [15] and the National Early Warning Score 2 (NEWS2) [16], respectively. Grade 2 (moderate) and grade 3 (severe) Covid-19 pneumonia were defined as radiological evidence of Covid-19 pneumonia in association with below or above a cutoff requirement of at least 3L/min supplemental oxygen to maintain a saturation of >96%, respectively. Patients with no radiological evidence of pneumonia at admission, or for whom radiological explorations were not performed, were defined as grade 1.

Outcomes.

The primary outcome of this study was time to unfavorable outcome, defined as: death, admission to an intensive care unit (ICU), or decision of non-admission to an ICU due to active care limitations, whichever came first.

Secondary outcomes were time to death, time to hospital discharge for a return home or in an aftercare and rehabilitation unit, fever and cough at day 5 and adverse events recorded in the patients receiving HCQ treatment.

Ethical considerations.

All patients provided oral informed consent to receive the drug and they did not object to the analysis of their data for research issues (non-opposition regime). The research protocol was reviewed and approved by the Ethics Committee of the French Infectious Diseases Society (Comité d'Ethique de Recherche en Maladies Infectieuses et Tropicales) under the Institutional Review Board N° IRB00011642. According to French law (n° 78-17 of 6 January 1978 on Computers, files and liberties), this study has been registered with the CNIL (French National Agency regulating Data Protection) and was conducted in compliance with the reference methodology 004).

Statistical analyses

Characteristics at admission of patients and biological parameters were described globally and according to the treatment group (HCQ vs SOC only). The results are expressed as mean (sd) or median [Q1-Q3] for quantitative variables and number (%) for qualitative variables. All statistical tests are bilateral and used a significance level of 5%. Crude comparisons of qualitative variables were conducted using Chi-2 tests or exact Fisher tests, as appropriate, and comparisons of quantitative variables were conducted using Student tests or non-parametric Wilcoxon tests, as appropriate. The clinically relevant outcomes (time to unfavorable event, time to death or time to hospital discharge for a return home or in an aftercare and rehabilitation unit) were compared using propensity score weighted analysis to balance the main baseline confounding factors between groups. The propensity score here corresponds to the probability that a patient receives HCQ treatment based on initial characteristics. It was estimated using a multivariate logistic model, including most relevant and *a priori* selected confounders: time between symptom onset and admission ≤ 7, Charlson comorbidity index, NEWS2 score at admission, pneumonia severity and medical history of arterial hypertension or obesity. Stabilized ATE weights were used [17]. Balance between groups for these factors was assessed by calculating the standardized difference after weighting. An absolute standardized difference < 0.1 was considered as an evidence of balance. For time-to-event outcomes, Kaplan-Meier curves according to treatment groups were plotted before and after weighting. Standard and weighted Cox proportional hazards regression models were fitted to estimate both crude and propensity score adjusted Hazard Ratio (HR) For binary outcomes, differences in risk between treatment groups [HCQ minus SOC only] were computed before and after propensity score weighting. For all outcomes, 95% CI were estimated and p-value corresponding to a robust Wald test were reported. Primary analysis involved HCQ patients who initiated HCQ treatment the day of admission or the day after, to avoid immortal time bias in favor of HCQ. In addition, we performed a sensitivity analysis on a wider population, also including the patients who initiated HCQ 2 days or more after admission. Finally, time to event was primarily defined as time from initiation of treatment for HCQ patients and time

from admission for the others; in subsequent sensitivity analyses, results were investigated considering a start time from admission for all patients.

Statistical analysis were carried out using R 3.6.3 software [https://cran.r-project.org/].

Results

Patients.

From January 28th, 2020, to March 19th, 2020, 117 patients with laboratory-confirmed Covid-19 infection were admitted. Among these, 18 were excluded from analysis due to having a contraindication to receiving HCQ (severe cardiopathy, n = 4; drug-drug interactions, n = 11; and pre-treatment elongated QT interval, n = 3) (figure 1). Overall, 42 patients were treated with HCQ 200mg x 3 and one patient was already receiving long-term HCQ at a 200mg bid dosage and the treatment was maintained. One patient treated by HCQ also received azithromycin (500mg/day) during 3 days due to concomittant *Salmonella spp* infection. Patients received HCQ for a median (IQR) treatment duration of 10 days (8-10). Five of these patients initiated HCQ treatment more than 2 days after hospital admission, and were therefore not included in the primary analysis but were kept in a sensitivity analysis.

The clinical and biological characteristics at admission of the 85 patients considered in the primary analysis are summarized in Table 1. In brief, 62% of patients were male, with a mean age of 66 (16) years. Patients had a median of 1 comorbidity, with a median (IQR) Charlson comorbidity index of 3 (2-5). Seventy percent were hospitalized within 7 days of symptom onset, had a median NEWS2 score of 3 (1-6) at admission and 73% presented with grade 2 or 3 pneumonia. Seventy-nine percent received concomitant antibiotics, and no patient received glucocorticosteroid therapy. Characteristics of patients included in the primary analysis according to treatment groups are summarized in Table 1. Overall, significantly more patients in the HCQ group presented with coughing than in the control group, and they had a significantly higher median heart rate and respiratory frequency.

Balance after propensity score weighting

Table 1 reports the standardized differences after propensity score weighting. All variables included in the propensity score model were well balanced. Despite the propensity weighting, differences persisted between groups for some baseline characteristics that could not be handled in the propensity score, namely a higher number of patients with altered mental status (given HCQ was firstly offered to patients able to give an informed consent) and a lower baseline cycle threshold on PCR at admission in the control group, but lower lymphocyte counts at admission in the HCQ group (there was a large amount of missing data on these last two factors: respectively 39% and 23%).

Primary outcome

Median follow-up of patients was 10 days (CI95% = [10-10]). 29 unfavorable events were considered in the time-to-event analysis. There were 18 transfers to ICU (8 among patients treated with HCQ and 10 in others) and 11 decisions of non-admission to an ICU due to active care limitations (5 in patients treated with HCQ and 6 in standard care only group). Overall, 3 patients treated with HCQ and 6 patients with standard care only died; for all of them a previous transfer to ICU or decision of active care limitation was recorded before. Results of primary and secondary outcomes in primary analysis are shown in Table 2. After propensity score weighting to balance confounding factors, treatment with HCQ was not associated with a significant reduction of the risk of unfavorable outcome compared to the standard care only group (HR 0.90 [0.38; 2.1], p = 0.81). (Figure 2)

Sensitivity analyses including patients who received HCQ after day 2 of admission (n = 5) yielded similar results (HR 0.81 [0.36; 1.83], p = 0.62). Considering time to event starting from admission did not change the conclusions either (cf Supplementary data).

Secondary outcomes (figure 3)

After adjusting for confounding factors, overall survival was not significantly different between the two groups (HR 0.89 [0.23; 3.47], p=0.86). Similarly, time to hospital discharge was not significantly different between the two groups (HR 1.18 [0.63; 2.22], p=0.61, cause-specific approach). At day five after admission, on the 44 patients that could be evaluated, there were no significant differences between the two groups with regards to cough (% after propensity score weighting: SOC alone: 56.3% vs HCQ: 60.6%, RD=4.26% [-20.3; 28.8], p=0.77) and fever (SOC alone: 23 % vs HCQ: 13.4%, RD= -9.6% [-23.9; 4.7], p=0.27).

The conclusions regarding secondary outcomes were unchanged while investigated in sensitivity analyses (cf Supplementary data).

Thirteen patients treated with HCQ (34%) underwent an ARDS (respectively 16 (35%) patients who received standard care only). At the end of follow-up, among patients alive: 38 returned home (HCQ: n=16, SOC: n=22), 9 were in a rehabilitation and care center (HCQ: n=5, Standard of care: n=4), 15 were in ICU (HCQ: n=7, Standard of care: n=8) and 13 were still hospitalized in the ward (HCQ: n=7, SOC: n=6). Among patients treated with HCQ, 6 patients (14%) reported side effects of HCQ, of which 4 (7%) resulted in premature discontinuation of treatment (corrected QT interval elongation, n = 2; cytopenia, n = 1; and paresthesia, n = 1). The 2 others side effects reported were headaches (n=1) and diarrhea (n=1).

Discussion

In this observational retrospective study, no significant reduction in the risk of unfavorable outcome was observed in patients hospitalized with Covid-19 treated with hydroxychloroquine as compared to SOC alone.

In a recent non-randomized study, Gautret et al. reported that treatment with HCQ at a 200 mg tid dosage was associated with higher rates of SARS–CoV-2 viral clearance after 6 days of treatment, particularly when associated with azithromycin, compared to an untreated control group consisting of patients from different medical centers [12]. However, some methodological flaws were noted that may affect the validity of the findings, notably a small sample size, the use of a control group which included patients with a contraindication to HCQ, and the exclusion prior to analysis of patients transferred to an ICU or deceased [18,19]. In a study with similar methodological limitations, Molina et al. report their experience with compassionate use of HCQ, also at a 200mg tid dosage in association with azithromycin, in 11 patients with moderate to severe Covid-19 (10 out of 11 required supplemental oxygen therapy). The authors found no evidence of rapid viral clearance, with 8/10 surviving patients still having positive PCR results at days 5 to 6 after treatment initiation[20]. Compared to most previous studies, we chose a clinical outcome, namely time to unfavorable outcome as the primary clinical endpoint, rather than surrogate markers of cure such as SARS-CoV2 viral clearance or time to clinical improvement, which we felt was a more pertinent marker of efficacy in this setting.

Our study has nonetheless several obvious limitations. The first major limitation is that the study was not randomized, and thus is open to potential biases. To address this weakness we performed a rigorous statistical analysis using propensity score weighting to control for main known confounders. Despite this propensity weighting, differences persisted between groups for some baseline characteristics, most notably regarding altered mental status, baseline lymphocyte counts, and baseline CT values for PCR. Finally, the small sample size also limits the power of our analyses. This sample size also limits the number of variables that could be included in the propensity score model,

so we carefully prespecified a list of the most important prognostic factors[21]. Our study population nevertheless reflects clinical practice in terms of the demographics of patients hospitalized at the beginning of the outbreak in France, i.e. primarily older patients with significant comorbidities.

Chloroquine and HCQ have previously shown promising results in the in vitro inhibition of a variety of viral pathogens in cell culture [22], including the SARS-CoV [23], but there have been to this day no successful translations to clinical efficacy in preventive or therapeutic clinical trials using HCQ as an antiviral agent [24,25]. Various dosing regimens for HCQ have been proposed in the treatment of Covid-19, and it is possible that using different doses may yield different results, in particular with the use of a loading dose on day 1 as is currently being evaluated in ongoing clinical trials [26]. Side-effects of HCQ were seldom reported in our study, although the retrospective nature of the study may lead to significant underreporting. There have however been valid concerns regarding the risk of cardiologic complications, namely ventricular arythmias and QT prolongation, related to the use of HCQ in the treatment of Covid-19, particularly in treating a condition already at risk of cardiovascular complications [27]. While the urgency of the current situation and lack of proven efficacy of any antiviral therapy against Covid-19 may justify the off-label use of treatments such as HCQ in selected cases, the authors would recommend exercising caution when extrapolating results of in vitro studies and preliminary clinical studies regarding the efficacy of HCQ against Covid-19, in light of the limited overall evidence to support its use and its potential cardiovascular side-effects.

In conclusion, in hospitalized adults with Covid-19, no significant reduction of the risk of unfavorable outcomes was observed with hydroxychloroquine in comparison to standard of care. Unmeasured confounders may however have persisted despite careful propensity-weighted analysis and the study might be underpowered. Ongoing controlled trials in patients with varying degrees of initial severity on a larger scale will help determine whether there is a place for hydroxychloroquine in the treatment of Covid-19.

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FIGURE LEGENDS:

Figure 1: Flow chart.

Figure 2 : Probability of survival without unfavorable outcomes.

Figure 3 : Probability of survival.

Table 1 : Clinical and biological characteristics at admission of the 85 patients considered in the primary analysis

Variable	Before Weighting						After Weighting		
	Global	**Standard of Care only (N=46)**		**HCQ (N=38)**		**p value †**	**Standard of Care only (N=46)**	**HCQ (N=38)**	**Standardized mean difference (%)**
		nb NA		nb NA					
Gender, M *	52 (62%)	-	31 (67%)	-	21 (55%)	0,25	59%	59%	0,01
Age, years *	65,5 ± 16	-	64,3 ± 17,9	-	67 ± 13,5	0,45	66,2 ± 17,1	67,1 ± 13,4	0,06
Charlson score *	3 [2-5] | 3,5 ± 2,2	-	3,6 ± 2,4	-	3,3 ± 1,9	0,55	3,6 ± 2,2	3,7 ± 2	0,02
Hospitalization < D7 symptoms, Yes *	59 (70%)	-	33 (72%)	-	26 (68%)	0,74	72%	76%	0,08
NEWS2 Score *	3 [1-6] | 3,6 ± 2,8	-	3,2 ± 3,1	-	3,9 ± 2,3	0,079	3,5 ± 2,8	3,3 ± 2,5	0,09
HTA, Yes *	29 (35%)	-	14 (30%)	-	15 (39%)	0,39	34%	35%	0,01
Obesity (BMI>30), Yes *	7 (8%)	-	3 (7%)	-	4 (11%)	0,7	6%	7%	0,02
Pneumonia severity, 1 *	23 (27%)	-	14 (30%)	-	9 (24%)	0,68	27%	28%	0,01
Pneumonia severity, 2 *	42 (50%)	-	23 (50%)	-	19 (50%)		49%	51%	0,04
Pneumonia severity, 3 *	19 (23%)	-	9 (20%)	-	10 (26%)		23%	21%	0,06
Diabetes, Yes	17 (20%)	-	9 (20%)	-	8 (21%)	0,87	15%	18%	0,09
Asthma/COPD, Yes	11 (13%)	-	6 (13%)	-	5 (13%)	1	18%	20%	0,04
Number of comorbidities	1 [0-2] | 1,4 ± 1,2	-	1,4 ± 1,2	-	1,3 ± 1,2	0,63	1,4 ± 1,1	1,2 ± 1,1	0,16
Symptoms									

Fever, Yes	43 (51%)	-	26 (57%)	-	17 (45%)	0,28	61%	31%	0,62
Cough, Yes	57 (68%)	-	25 (54%)	-	32 (84%)	0,004	59%	84%	0,55
Headaches, Yes	15 (18%)	-	5 (11%)	-	10 (26%)	0,07	13%	21%	0,21
Diarrhea, Yes	8 (9%)	-	3 (7%)	-	5 (13%)	0,46	5%	29%	0,65
Mental confusion, Yes	12 (14%)	-	10 (22%)	-	2 (5%)	0,032	23%	5%	0,53
Anosia, Yes	1 (1%)	-	1 (2%)	-	0 (0%)	1	3%	0%	0,23
Dyspnea, Yes	43 (51%)	-	18 (39%)	-	25 (66%)	0,015	48%	64%	0,32
Oxygen									
O2, ml/min	0 [0-2] | 1,3 ± 1,6	-	1,2 ± 1,8	-	1,4 ± 1,3	0,15	1,2 ± 1,7	1,2 ± 1,3	0,03
Vital and biological parameters									
O2 Saturation	96 [95-97] | 96 ± 2,2	-	96,7 ± 1,9	-	95,1 ± 2,2	0,001	96,5 ± 2	95,3 ± 2	0,61
Respiratory rate	20 [14-24] | 19,3 ± 5,3	2	17,9 ± 5,4	-	21 ± 4,9	0,007	18,3 ± 5	20,4 ± 5,1	0,42
Heart rate	82 [72-92] | 82,6 ± 13,4	-	80,1 ± 12,9	-	85,5 ± 13,7	0,04	79,8 ± 13,1	84,4 ± 15	0,33
CRP	57 [21-113] | 74,7 ± 66,4	21	68,7 ± 66,4	6	79,3 ± 67,2	0,61	66,8 ± 64,7	82,7 ± 69,7	0,24
Lymphocyts	1,1 [0,8-1,3] | 1,2 ± 0,6	16	1,3 ± 0,7	3	1 ± 0,4	0,032	1,3 ± 0,6	1 ± 0,5	0,53
Virology									
CT mesured at diagnosis PCR	20,6 [18,7-26,8] | 22,1 ± 4,7	20	20,7 ± 4,2	13	23,5 ± 4,9	0,018	20,4 ± 4,1	23 ± 5,3	0,56

* Only these variables were included in the model to estimate the propensity score

† Chi-2 (or eaxct Fisher test) was used for qualitative variables and Student test (or non-parametric Wilcoxon test) for quantitative variables

Table 2: Primary and secondary outcomes in the Primary analysis population

Outcomes	Standard of Care only		HCQ		Crude analysis without IPTW weighting		IPTW-weighted analysis	
Time to events outcomes	**N patients**	**n events**	**N patients**	**n events**	**HR [CI95%]**	**p**	**HR [CI95%]**	**p †**
Unfavorable outcome (ICU, limitation or death)	46	16	38	13	1.04 [0.5; 2.17]	0.91	0.90 [0.38; 2.1]	0.81
Death	46	6	38	3	0.66 [0.16; 2.64]	0.55	0.89 [0.23; 3.47]	0.86
Hopital discharge for home or aftercare and rehabilitation center	46	26	38	21	0.87 [0.49; 1.56]	0.64	1.18 [0.63; 2.22]	0.61
Symptoms at clinical evaluation of day 5	**N patients**	**n (%)**	**N patients**	**n (%)**	**Risk Difference HCQ - SOC [CI95%]**	**p**	**Risk Difference HCQ - SOC [CI95%]**	**p †**
Cough	24	13 (54%)	20	13 (65%)	10.8% [-18.1; 39.7]	0.46	4.3% [-20.3; 28.8]	0.77
Fever	24	5 (21%)	20	4 (20%)	-0.8% [-24.7; 23.1]	0.95	-9.6% [-23.9; 4.7]	0.27

† Wald test performed using a robust estimator of variance

SOC: Standard of Care only; p: p value; HR: Hazard Ratio

Figure 1

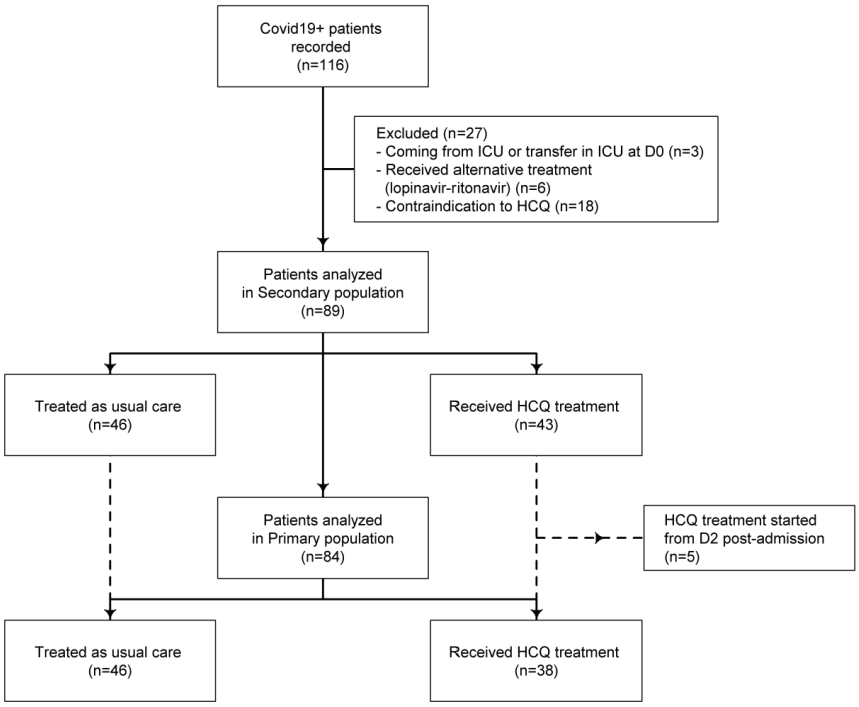

Covid19+ patients recorded (n=116)
Excluded (n=27)
- Coming from ICU or transfer in ICU at D0 (n=3)
- Received alternative treatment (lopinavir-ritonavir) (n=6)
- Contraindication to HCQ (n=18)
Patients analyzed in Secondary population (n=89)
Treated as usual care (n=46)
Received HCQ treatment (n=43)
Patients analyzed in Primary population (n=84)
HCQ treatment started from D2 post-admission (n=5)
Treated as usual care (n=46)
Received HCQ treatment (n=38)

Figure 2

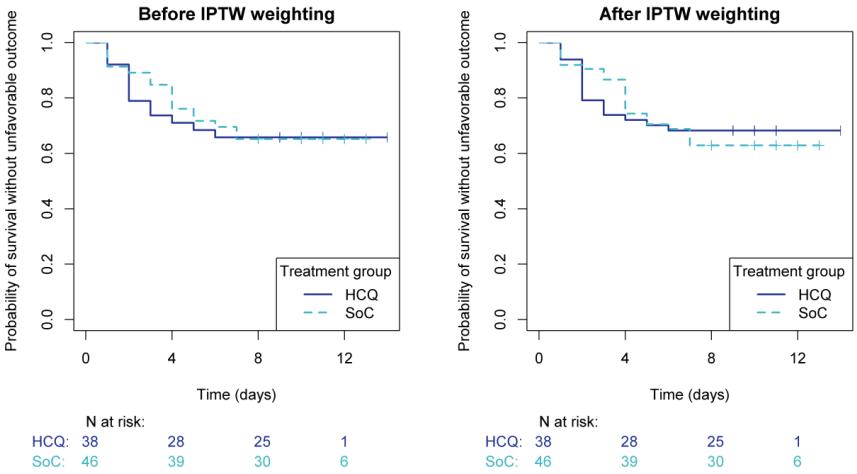
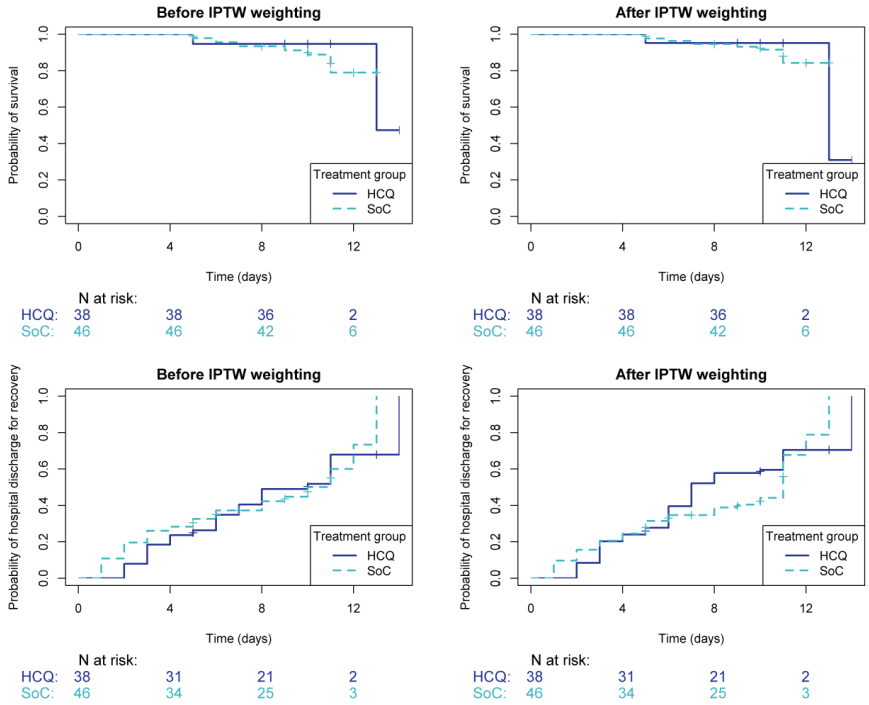

Before IPTW weighting
Probability of survival without unfavorable outcome
0.0
0.2
0.4
0.6
0.8
1.0
0
4
8
12
Time (days)
Treatment group
HCQ
SoC
N at risk:
HCQ: 38 28 25 1
SoC: 46 39 30 6
After IPTW weighting
Probability of survival without unfavorable outcome
0.0
0.2
0.4
0.6
0.8
1.0
0
4
8
12
Time (days)
Treatment group
HCQ
SoC
N at risk:
HCQ: 38 28 25 1
SoC: 46 39 30 6

Figure 3


Before IPTW weighting
Probability of survival
Treatment group
HCQ
SoC
Time (days)
N at risk:
HCQ: 38 38 36 2
SoC: 46 46 42 6
After IPTW weighting
Probability of survival
Treatment group
HCQ
SoC
Time (days)
N at risk:
HCQ: 38 38 36 2
SoC: 46 46 42 6
Before IPTW weighting
Probability of hospital discharge for recovery
Treatment group
HCQ
SoC
Time (days)
N at risk:
HCQ: 38 31 21 2
SoC: 46 34 25 3
After IPTW weighting
Probability of hospital discharge for recovery
Treatment group
HCQ
SoC
Time (days)
N at risk:
HCQ: 38 31 21 2
SoC: 46 34 25 3